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Synthesis of novel nitrogen ligands and their application to transition metal catalyzed reactions

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Synthesis of novel nitrogen ligands and their application to transition metal catalyzed reactions

COMO

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0.1 Foreword

Coordination Chemistry is the chemistry of metal complexes (or coordination compounds) which consist of a central metal ion surrounded by a certain number of molecules or ions, called ligands.

The ligands are bounded via dative or coordinative bonds to the central metal ion and the total number of the sites occupied by them identifies the coordination number of the metal.

In some cases, more than one of these sites is occupied by the same ligand when the ligand acts as polydentate ligand.

The role of a metal complex used in a reaction as catalyst is fundamental, since many processes only take place when the catalyst offer new reaction pathways.

In the last decades many have been the problems that chemists tried to overcome, from both scientific and industrially point of view; such as the need to simplify the way of synthesis of the ligands, and the possibility to apply a combinatorial approach in order to find suitable catalysts in a easier and faster way.

Supramolecular Chemistry answers these needs.[1]

One of the cornerstone of Supramolecular Chemistry is that ligands contain, besides the atom(s) coordinated to the catalytic metal center, an additional functionality capable of non-covalent interactions which can play the following roles:

- allow monondentate ligands to self-assemble into the so-called "supramolecular polydentate ligands",
- bind the substrate(s) in proximity to the catalytic metal center, in analogy to metalloenzymes.

In both cases, this approach causes reduced degrees of freedom in the metal coordination complexes, which are thus expected to result in more pre-organized systems with a better capacity of controlling the metal-catalyzed reaction.

In chapter 1 and 2 will be highlighted the use of hydrogen bonding as non-covalent force able to create supramolecular bidentate ligands.

In the last few years, indeed, several powerful supramolecular bidentate ligands with outstanding reactivity and selectivity have been described, but unfortunately this concept has so far been exclusively confined to the use of phosphorus ligands.

[1] S. Carboni, C. Gennari, L. Pignataro, U. Piarulli, *Dalton Trans.* **2011**, *40*, 4355.

So it will be described the hydrogen bonds-induced formation, characterization and application to transition metal catalyzed transformations, of supramolecular bis(oxazoline) and phosphinooxazoline ligands (Figure 0.1 and Figure 0.2).

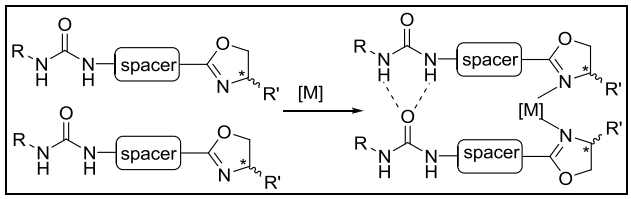


Figure 0.1

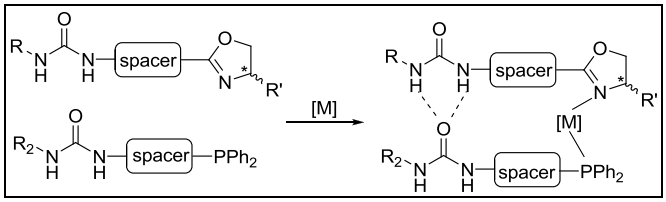


Figure 0.2

The formation of our transition metal complexes (Cu^{2+}, Pd^{2+}, Zn^{2+} and Ir^{+}) was investigated by complexation studies through the use of different techniques, such as mass spectrometry, UV/Vis and NMR spectroscopy.

In addition, recently, particular attention has been paid to solve another drawback of the application of metal-complexes, the majority of which contains expensive noble metals (Ru, Rh, Ir, Pd, Pt). It concerns the high cost of the metals, which has serious affect on the application in industrial scale. Therefore, quite obviously, the replacement of precious metals with cheap first-row transition metals turns out in a great breakthrough.[2]

Among the possible suitable metals, we chose iron, in particular Fe(II), because it owns important advantages: iron is a physiologically and environmentally friendly metal and it is abundant and cheap.

[2] *Iron Catalysis in Organic Chemistry: Reactions and Applications*, Wiley-VCH, **2008**; R. H. Morris, *Chem. Soc. Rev*. **2009**, *38*, 2282; R. M. Bullock, *Catalysis without Precious Metals*, Wiley-VCH, **2010**.

Regrettably, Fe(II)-complexes cannot be often considered robust catalyst. Indeed Fe(II) is very prone to oxidation to Fe(III).

Polydentate nitrogen ligands, are expected to stabilize Fe(II) and, therefore, we paid attention on tridentate N_3-ligands and tetradentate N_4-ligands in order to form iron(II)-complexes (Figure 0.3).

The formation of our complexes will be discussed in chapter 3.

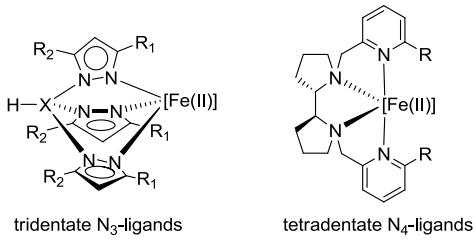


Figure 0.3

The characterization of the iron(II)-complexes that we prepared, mainly relied on mass spectrometry, since the NMR spectroscopy appeared quite often as not a suitable technique, due to the paramagnetism of the Fe(II)-species.

Preliminary attempts in order to study the application of the complexes in hydrogenation and epoxidation reactions were done and described in chapter 3, although studies are still underway in our laboratory.

Chapter 1

Chiral Supramolecular Bisoxazoline Ligands

1.1 Asymmetric catalysis

The biological activity of many pharmaceutical compounds, agrochemicals, flavors, and fragrances is associated with absolute molecular configuration.

Since van't Hoff and Le Bel around 140 years ago introduced the tetrahedral model of the carbon atom to explain the optical activity of organic molecules, providing a structural basis for molecular stereochemistry, scientists have been fascinated by the challenge to achieve absolute stereocontrol in chemical transformations starting from achiral compounds.

Chirality has been denoted as "signature of life", and it is not unexpected that questions on the origin, control and amplification of homochirality are intimately associated with chemical evolution and the origin of life.

In spite of the incredible importance, asymmetric catalysis has not been considered as a fundamental research area until 1968.

Besides enzymatic processes, only few examples of enantioselective catalytic reactions were known at that time and, in view of the generally low enantiomeric excesses, many chemists actually doubted that synthetic chiral catalysts would had ever played an important role in asymmetric synthesis.

Soon the situation dramatically changed, when impressive progresses were made in the rhodium-catalyzed hydrogenation of olefins by Knowles,[3] Horner[4], Kagan[5] and Noyori,[6] culminating in the famous Monsanto process for L-DOPA and in the selective epoxidation[7] and dihydroxilation[8] of olefins by Sharpless.

The demand for chiral compounds, predominantly as single enantiomers, has sharply escalated in recent years, particularly driven by the demands of the pharmaceutical industry, but also by other applications, including agricultural chemicals, flavors, fragrances, and materials.

We have only to realize that two-thirds of prescription drugs are chiral, with the majority of new chiral drugs being single enantiomers, especially since when, in 1992, the Food and Drug

[3] W. S. Knowles, M. J. Sabacky, *Chem. Commun.* **1968**, *22*, 1445; W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *J. Chem. Soc., Chem. Commun.* **1972**, 10; B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946; W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998.
[4] L. Horner, H. Siegel, H. Büthe, *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 941.
[5] H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429.
[6] R. Noyori, *Adv. Synth. Cat.* **2003**, *345*, 15.
[7] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765; M. G. Finn, K. B. Sharpless, *J. Am. Chem. Soc.* **1991**, *113*, 113.
[8] H. C. Kolb, M. S. van Nieuwenhze, K. B. Sharpless, *Chem. Rev.*, **1994**, *94*, 2483.

Administration of the USA published a policy statement for the development of the new stereoisomeric drugs.[9]

In the last two decades, the number of new chiral compounds submitted for approval to various regulatory bodies as single enantiomers, rather than as racemic mixtures, has been rapidly increasing and the trend for future drug developments is evident. The need to synthesize active pharmaceutical ingredients (API) as a single isomer has promoted a variety of methodologies to achieve the goal.[10]

Among the numerous variables, cost usually plays a key role in the decision of the best route, as well as environmental and safety issues.

Although bio-related applications are the most obvious, materials science also relies on the properties imparted by chirality, notably in chiral polymers and liquid crystals.

Asymmetric catalysis is an integrated chemical approach in which the maximum chiral efficiency can be obtained only by a combination of suitable molecular design with proper reaction conditions. The reaction must proceed with high turnover number (TON) and high turnover frequency (TOF), while the enantioselectivity range is between 50:50 (nonselective) and 100:0 (perfectly selective).

By now it is, in principle, the most efficient strategy for the production of enantiopure compounds, requiring only catalytic amounts of chirally modified metal complexes formed by a metal source and one or more chiral ligands. Chiral ligands modify intrinsically the metal atoms. They must possess suitable three-dimensional structure and functionality to generate sufficient reactivity and the desired stereoselectivity. In this way, a chiral catalyst can permit kinetically precise discrimination among the enantiotopic atoms, groups or faces in chiral molecules.[11]

Two significant challenges pertain to asymmetric catalysis: discovering new catalytic reactions and inventing effective chiral catalysts.

Thousands of chiral ligands have been prepared so far, although a relatively small number of structural classes stand out because of their broad applicability. A survey of their structures reveals that, at first sight, a surprisingly large number of them possess C_2 symmetry, such as for instance, the C_2-symmetric ligand DIOP, introduced by Dang and Kagan in 1971.[12]

[9] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm
[10] V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *106*, 2734.
[11] P. Espinet, K. Soulantica, *Coord. Chem. Rev.* **1999**, *193-195*, 499.
[12] T. P. Dang, H. B. Kagan, *J. Chem. Soc. Chem. Commun*. **1971**, 481.

The reason of choosing a C_2-symmetric ligand is generally related to the reduction of the number of possible isomeric metal complexes, as well as the number of different substrate-catalyst arrangements and reaction pathways, if compared with a non-symmetrical ligand.
Because fewer reaction intermediates must be taken into account, C_2-symmetry is of particular advantage in mechanistic studies because it facilitates the analysis of ligand-substrate interactions that may be responsible of the enantioselection. Initially, chiral ligands were developed containing mainly phosphorus donor atoms; later the concept of C_2-symmetry was successfully applied also to other ligand classes with N or O donor atoms.[13]

1.2 Supramolecular approach

At the turn of the 20th century, the concept of supramolecular chemistry was introduced for the first time.
Emil Fischer, a German chemist, studying the reaction of an enzyme with a substrate, came up with the conclusion that the shape of a substrate molecule needed to be complementary with the shape of its receptor site in order to recognize it and then react. For this finding, he was awarded the Nobel Prize in Chemistry in 1902. This principle led to an increasing understanding of many biological processes, such as the structure of the proteins and the elucidation of the DNA double helical interaction. Nearly 100 years later, chemists were able to take these concepts and apply them to synthetic systems.
In particular, Jean-Marie Lehn, Nobel Prize in Chemistry in 1987, provided the concept of supramolecular chemistry as "chemistry beyond the molecule", whereby organized entities of higher complexity result from the association of two or more chemical species held together by intermolecular additive and cooperative forces including hydrogen bonding, coordination, hydrophobic interactions, π-π interactions, electrostatic interactions of a reversible nature.
Of remarkable impact was to realize that the final properties of a supramolecular molecule are different from the sum of the properties of each individual component.

Supramolecular chemistry is a multidisciplinary field which impinges on various disciplines, such as the traditional areas of organic and inorganic chemistry, needed to synthesize the precursors for a supramolecule, physical chemistry, to understand the

[13] A. Pfaltz, *Acc. Chem. Res.* **1993**, 26**,** 339; A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9,* 1; Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155.

properties of supramolecular systems and computational modeling to understand supramolecular complex behavior.

Supramolecular chemistry can be split into two big categories, arbitrarily named *host-guest chemistry* and *self-assembly chemistry*.

In the *host-guest chemistry* the host is the largest molecule and the guest the smallest. The host molecule recognizes the best guest molecules among those containing the array of binding sites and steric features that complement those of the host. Thus, guest and host must be compatible with respect to the shape if they must be complexed. This family includes many biological systems, among them it is worth mentioning the system enzyme-substrate.

Where there is no significant difference in size and no species is acting as a host for another, the non-covalent joining is named *self-assembly*. Specifically, the *self-assembly* is the equilibrium between two or more molecular components to produce an aggregate with a structure dependent only on the characteristic of the chemical building blocks.

Hereunder, *self-assembly* chemistry will be exclusively discussed, since it is the approach that SupraBox formation is based upon.

1.3 *Self-assembly* chemistry

Examples of *self-assembly* can be found in different fields, from chemistry to biology, biochemistry or nanotechnologies.

It consists in the spontaneous association of two or more species to create a larger aggregate through the formation of reversible, supramolecular interactions.

DNA double-helix is probably the best-known self-assembled structure in biological system. It is made of complementary strands entwined *via* hydrogen bonds and π-π stacking. The strands recognize each other and join together to form the most thermodynamically stable assembly product.

Folding process of proteins to give rise to secondary, tertiary and quaternary structures, as well as hydrophobic effect in the formation and activity of lipid membranes, or RNA interactions in the structure of Virus, like tobacco mosaic virus (TMV), operate in a broadly similar manner.

Such biological examples have provided a powerful incentive for researchers to explore molecular associations more broadly and also giving birth to the *supramolecular chemistry*, a rapidly expanding field of chemistry.

Synthetic self-assembly systems are based on the ability of the chemists to design molecules containing complementary functionalities. A chemist has in principle no direct control over the assembly process otherwise it would not be termed *self*-assembly. However it is possible to induce the chemical system to rearrange to the most thermodynamically stable (and desired) product, by a careful and judicious choice of the different parts of the system.

1.4 Formation of synthetic bidentate ligands by *self-assembly*

The use of non-covalent supramolecular ligand–ligand interaction in transition metal-catalyzed transformations is a new, rapidly emerging area of research. The basic idea is to use two monodentate ligands, which can imitate the situation of a bidentate ligand at the catalytically active metal center through non-covalent connections between the two respective binding sites. For this reason, besides the atom coordinating the catalytic metal, the monodentate ligands need additional functionalities capable of ligand–ligand bonding *via* non-covalent interactions, such as hydrogen bonding, dipole-dipole, charge transfer, van der Waals, π-π stacking, and inclusion compounds.[14] This approach offers the advantage of an easier synthesis, compared to the synthesis of covalent bidentate ligands, and of reduced degrees of freedom in the respective metal coordination complexes, compared to the analogs complexes based on monodentate ligands. This is expected to result in a more pre-organized systems with a better capacity of controlling the metal-catalyzed reaction, thus imparting higher activity and chemo-, regio-, and stereoselectivity to the corresponding transition metal complexes in a number of catalytic applications.[15]

1.5 *Self-assembly* through hydrogen bonding

The concept of hydrogen bonding was firstly introduced in the literature in 1920 by Latimer and Rodebush to describe the nature of association in the liquid state of water.[16] Indeed, a footnote in their paper credited: "Mr. Huggins (a first-year graduated student of this

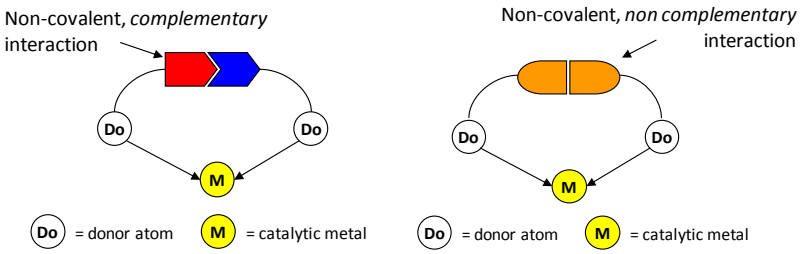
[14] Annu. Rep. Prog. Chem., Sect. A: Inorg. Chem., **2012**, 108, 292; Annu. Rep. Prog. Chem., Sect. B:Org. Chem., **2012**, 108, 171.
[15] B. Breit, *Angew. Chem. Int. Ed.* **2005**, 44, 6816; M. J. Wilkinson, P. W. N. M. van Leeuwen, J. N. H. Reek, *Org. Biomol. Chem.* **2005**, *3*, 2371; A. J. Sandee, J. N. H. Reek, *Dalton Trans.* **2006**, 3385; P. W. N. M. van Leeuwen, *Supramolecular Catalysis*, Wiley-VCH, Weinheim, **2008**; P. E. Goudriaan, P. W. N. M. van Leeuwen, M.-N. Birkholz, J. N. H. Reek, *Eur. J. Inorg. Chem.* **2008**, 2939; G. Gasparini, M. Dal Molin, L. J. Prins, *Eur. J. Org. Chem.* **2010**, 2429; J. Meeuwissen, J. N. H. Reek, *Nat. Chem.* **2010**, *2*, 615–621;C. Gennari, U. Piarulli, *Dalton Trans.* **2011**, 40, 4355; J. N. H. Reek, *Org. Biomol. Chem.* **2011**, 9, 1704.
[16] W. M. Latimer, W. H. Rodebush,, *J. Am. Chem. Soc.*, **1920**, *42*, 1419.

laboratory) has used the idea of a hydrogen kernel held between two atoms as a theory in regard to certain organic compounds".

Among the different kinds of non-covalent interactions used so far for the *self-assembly*, hydrogen bonds are arguably the most practical and efficient for several reasons:

- functional groups capable of hydrogen bonding (*e.g.* ureas, amides, guanidines) are stable and relatively easy to introduce;
- hydrogen bonds are created dynamically and reversibly in the reaction medium, thus being able to self-repair when broken;
- often coexist with other interactions in a 'non-invasive' manner.

The interaction can be of two different nature: *complementary* or *non complementary*, depending on the nature of the groups responsible of the hydrogen bonds formation. (Scheme 1.1).



Scheme 1.1

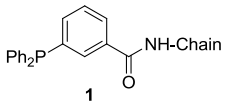
In case of *complementary* interactions, one of the two ligands has functionalities which make it able to act as hydrogen-bond donor while the other one as hydrogen-bond acceptor. In case the interaction is *non complementary*, both ligands can act as hydrogen bond acceptor and donor.

Hereafter is reported a brief introduction on some common examples of supramolecular synthetic organic systems through hydrogen bonding.

1.5.1 Hydrogen bonding among amido groups

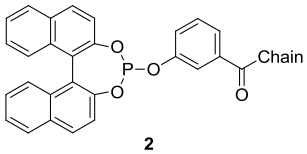
Peptides are the class that probably possesses the best known functionality capable of intermolecular and intramolecular backbone interaction by hydrogen bonding.

Breit recently developed a library of phosphines **1** and phosphites **2**,[17] that mimic the well-known PhanePhos ligand.[18] *Meta*-carboxypeptidyl-substituted triarylphosphines or phosphites were employed to construct PhanePhos-like structures by means of an inter-ligand helical hydrogen-bonding network. The latter, in turn, induces a planar π-stacking arrangement of the two *meta*-substituted arene rings which resembles the planar stereogenic element present in PhanePhos, as it was demonstrated by X-ray and NMR analysis of Pt- and Rh-complexes. The homocombinations of ligands **1** and **2**, in the presence of $[Rh(cod)_2BF_4]$, were tested in the enantioselective hydrogenation of methyl 2-acetamido acrylate, methyl (*Z*)-2-acetamido cinnamate and dimethyl itaconate. The best combinations gave enantioselectivity levels comparable with those of PhanePhos ligands (75- 99% ee).



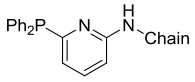
1

a Chain = Val-Val-OMe
b Chain = Val-Ala-OMe
c Chain = t-Leu-Val-OMe
d Chain = Gly-OEt
e Chain = Val-OMe
f Chain = Val-NH*n*Bu
g Chain = Ala-Val-OMe
h Chain = *D*Val-*D*Val-OMe
i Chain = OMe
j Chain = NHBz



2

(*S*)-**a** Chain = NH-Val-Val-OMe
(*R*)-**b** Chain = NH-Val-Ala-OMe
(*R*)-**c** Chain = OMe

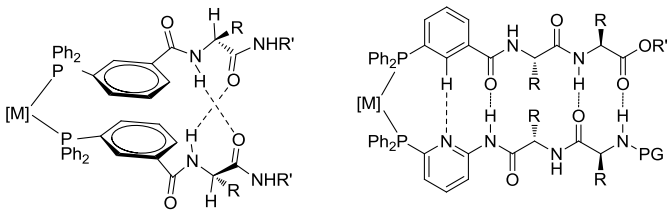


3

a Chain = Val-Val-Boc
b Chain = Ala-Val-Boc
c Chain = Val-Fmoc
d Chain = Ala-Fmoc
e Chain = Val-Moc
f Chain = Ala-Moc
g Chain = Piv
h Chain = COBz

The concept of utilizing peptide-functionalized *P*-ligands was further developed and expanded to the formation of heterocomplexes.[19] Indeed, when *C*-linked peptides **1** were combined with *N*-linked peptides **3** in the presence of Pt(II) and Rh(I) salts, a two-stranded, antiparallel β-sheet structure was formed (Scheme 1.2), which served as basis for the generation of a heterobidentate ligand library.

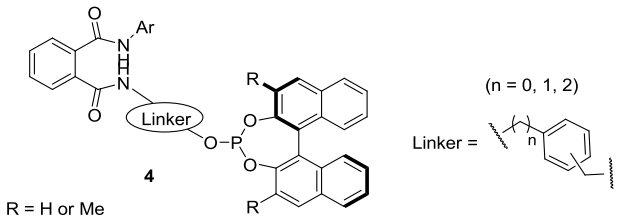
[17] A. C. Laungani, B. Breit, *Chem. Commun.* **2008**, 844.
[18] P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, P. J. Reider, *J. Am. Chem. Soc.*, **1997**, 119, 6207; P. J. Pye, K. Rossen, R. A. Reamer, R. P. Volante, P. J. Reider, *Tetrahedron Lett.*, **1998**, 39, 4441.
[19] A. C. Laungani, J. M. Slattery, I. Krossing, B. Breit, *Chem.–Eur. J.* **2008**, *14*, 4488.



Scheme 1.2

These heterocomplexes were screened in the enantioselective hydroformylation of styrene. Remarkably, the stereocenters of the peptide chains could induce a moderate selectivity, although they were remote from the catalytic metal centre.

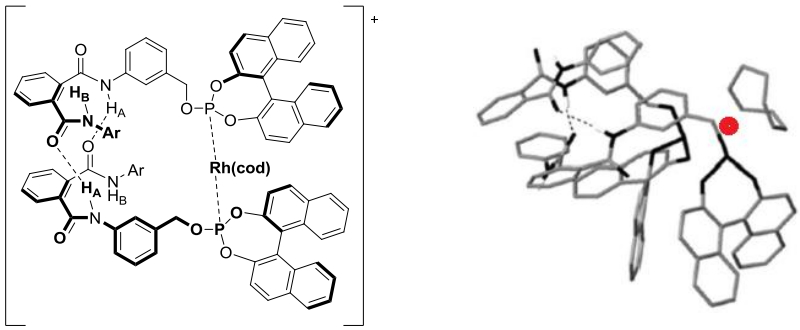
In a recent project developed by the group of Gennari and our group, the formation of a new supramolecular bidentate phosphorous ligands was investigated, starting from a new class of chiral monodentate phosphite ligands **4**, named PhtalaPhos, which contain a phthalic acid secondary diamide moiety.[20]



Phtalamidic group displays both donor and acceptor hydrogen-bonding properties that, in principle, can give rise to supramolecular interactions between the two ligands and with the substrate of the reaction.

These ligands were applied to the rhodium-catalyzed enantioselective hydrogenation of olefins with excellent results and enantioselectivities (up to >99%). Computational studies were also made to investigate the real structure of the precatalyst and the effective double hydrogen bond array. (Scheme 1.3)

[20] L. Pignataro, S. Carboni, M. Civera, R. Colombo, U. Piarulli, C. Gennari, *Angew. Chem. Int. Ed*. **2010**, *49*, 6633.

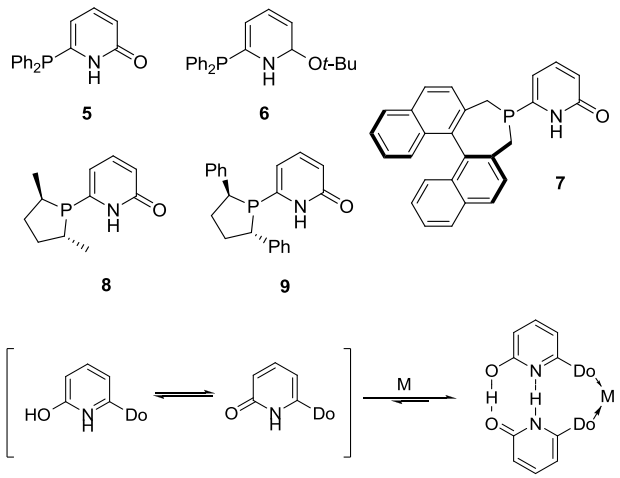


Scheme 1.3

1.5.2 Hydrogen bonding among heterocycles

The first example concerning the *in situ* generation of bidentate ligands based on s*elf-assembly* through hydrogen bonding of monodentate ligands in the coordination sphere of a metal center is attributed to Breit and Seiche.[21]

They developed a number of phosphines **5-9** using as hydrogen bond source the already well-known equilibrium between the two tautomeric forms of the 2-hydroxypyridine derivatives.[22] (Scheme 1.4)



Scheme 1.4

[21] B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608; W. Seiche, A. Schuschkowski, B. Breit, *Adv. Synth. Catal.* **2005**, *347*, 1488; B. Breit, W. Seiche, *Pure and Appl. Chem.* **2006**, *78*, 249: B. Breit, W. Seiche, *Angew. Chem. Int. Ed.*, **2005**, *44*, 1640.

[22] K. Mashima, H. Nakano, A. Nakamura, *J. Am. Chem. Soc.* **1993**, *115*, 11632; K. Mashima, M. Tanaka, K. Tani, H. Nakano, A. Nakamura, *Inorg. Chem.* **1996**, *35*, 5244.

Ligands **5-9** were used in Rhodium-catalyzed hydrogenation of olefins with enantioselectivity up to 99%.

The importance of the tautomeric equilibrium was settled by the poor results obtained with ligand **6**, unable to self-assemble. Moreover, they observed that the hydrogen-bonding network of the ligands, and thus the chelating binding mode, can be disrupted by employing either temperatures above 110°C or protic solvents such as methanol and acetic acid.

Breit also explored the possibility to exploit tautomeric interactions in a combinatorial fashion. Inspired by DNA base pairing, the method enables rapid generation of catalyst libraries by simple mixing of the components without additional synthetic steps, and so allowing access towards structurally diverse and meaningful ligand libraries

The DNA approach, or rather a non-tautomeric system based on Adenine-Thymine interplay, was used to overcome the problem of statistic mixture (Figure 1.1).[23]

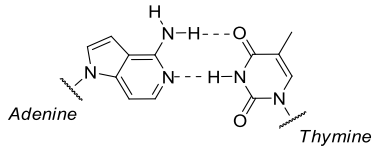
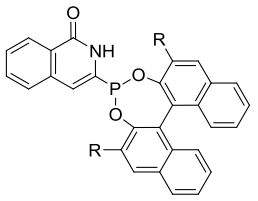


Figure 1.1

A library of 8 building blocks were synthesized to obtain heterocomplexes, which form stable hydrogen bonding even in protic solvents such as methanol. Tautomeric and non-tautomeric systems were then used in a various list of reactions like hydrogenation,[24] *anti*-Markovnikov hydration of terminal alkynes,[25] hydration of nitriles,[26] allylic amination[27] and hydrocyanation of alkenes.[28]

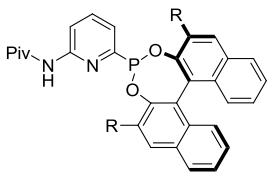
Phosphonites **10** and **11** were then introduced using a BINOL moiety in order to create the chiral ligand donor group and tested in the hydrogenation of olefins.[29]

[23] C. Waloch, J. Wieland, M. Keller, B. Breit, *Angew. Chem. Int. Ed.* **2007**, *46*, 3037.
[24] M-N. Birkholz, N. V. Dubrovina, H. Jiao, D. Michalik, J. Holz, R. Paciello, B. Breit, A. Borner, *Chem. Eur. J.*, **2007**, *13*, 5896.
[25] F. Chevallier, B. Breit, *Angew. Chem. Int. Ed.*, **2006**, *45*, 1599.
[26] T. Smejkal, B. Breit, Organometallics, **2007**, *26*, 2461.
[27] M-N. Birkholz, N. V. Dubrovina, I. A. Shuklov, J. Holz, R. Paciello, C. Waloch, B. Breit, A. Borner, *Tetrahedon: Asymmetry*, **2007**, *18*, 2055. I. Usui, S. Schmidt, M. Keller, B. Breit, *Org. Lett.*, **2008**, *10*, 1207.
[28] M. De Greef, B. Breit, *Angew. Chem. Int. Ed.*, **2009**, *48*, 551.
[29] M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188.



10

(*S*)-**a** R = H
(*R*)-**b** R = H
(*S*)-**c** R = Me



11

a R = H
b R = Me
c R = *p*-tolyl

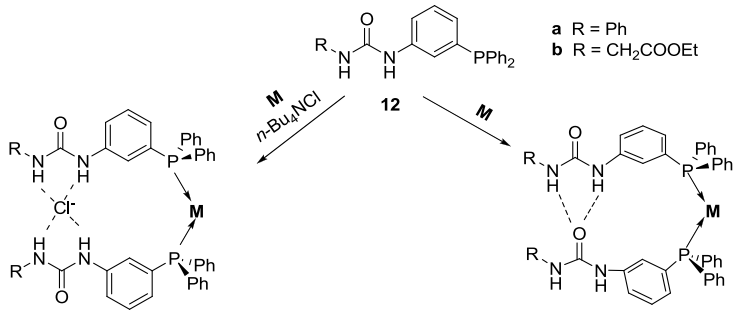
1.5.3 Hydrogen bonding between urea functionalities

Ureas are functionalities well known to form network of hydrogen bonds, and have been used over the last years as additional interacting functionalities for the formation of supramolecular bidentate ligands. The groups of Love[30] and Reek[31] had a key-player role in this field.

They firstly, independently described the formation of transition metal complexes containing urea-phosphine ligands **12** in the presence of a palladium source.

In particular, with ligand **12a** Love observed the formation of a species assumed to have a polymeric nature with intermolecular hydrogen bonding due to its insolubility in commonly used solvents; whereas Reek, with ligand **12b**, reported the formation of a *trans* complex.

In addition, in the presence of a metal source and tetrabutylammonium chloride, symmetric supramolecular metal complexes were obtained, where a chloride ion was accommodated between the two urea groups through a network of four hydrogen bonding (Scheme 1.5).

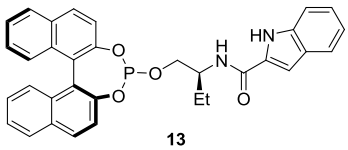


Scheme 1.5

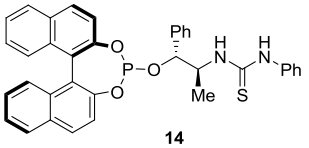
[30] P. A. Duckmanton, A. J. Blake, J. B. Love, *Inorg. Chem.* **2005**, *44*, 7708.
[31] L. K. Knight, Z. Freixa, P. W. N. M. van Leeuwen, J. N. H., Reek, *Organometallics* **2006**, *25*, 954.

Later, Reek and co-workers developed a new class of chiral urea-functionalized phosphite and phosphoramidite ligands **13-28** called UREAphos, capable of self-assembling in the presence of a rhodium source for the formation supramolecular homocomplexes, as confirmed by NMR studies.

The rhodium complexes of the UREAphos ligands were screened in the enantioselective hydrogenation of both benchmark substrates and challenging, industrially relevant olefins.[32]



13



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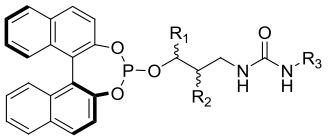
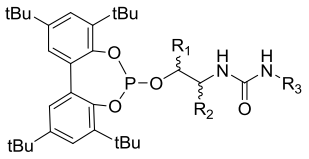
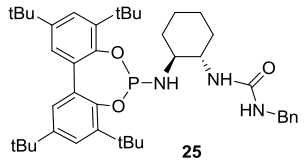


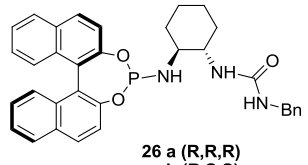
15 (R) R_1: H, R_2: H, R_3: Pr
16 (R) R_1: H, R_2: Me, Me, R_3: Ph
17 (R) R_1: H, R_2: H, R_3: Bn
18 (R,S,R) R_1: Ph, R_2: Me, R_3: Ph
19 (R) R_1: H, R_2: Et, R_3: Ph
20 (R) R_1: H, R_2: Me, R_3: Bn
21 (R) R_1: H, R_2: Me, R_3: Ph
22 (R,R) R_1: H, R_2: Me, R_3: nBu



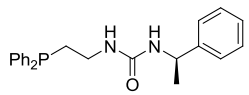
23 (S) R_1: H, R_2: iPr, R_3: Ph
24 (S) R_1: H, R_2: Me, R_3: Bn



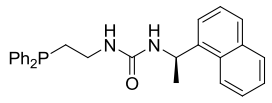
25



26 a (R,R,R)
b (R,S,S)



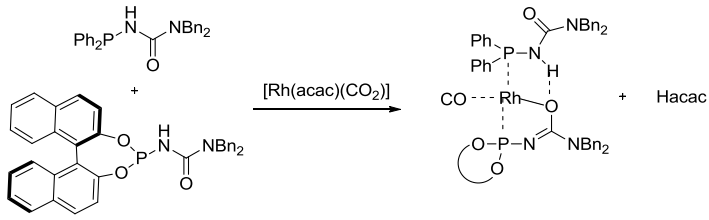
27



28

Recently, 6 phosphinourea ligands were used in a combinational fashion to form 14 supramolecular rhodium catalysts: 6 homocomplexes and 8 heterocomplexes (Scheme 1.6).[33]

[32] A. J. Sandee, A. M. van der Burg, J. N. H. Reek, *Chem. Commun.* **2007**, 864; J. Meeuwissen, M. Kuil, A. M. van der Burg, A. J. Sandee, J. N. H. Reek, *Chem. Eur. J.* **2009**, 15, 10272.
[33] J. Meeuwissen, A. J. Sandee, B. de Bruin, M. A. Siegler, A. L. Spek, J. N. H. Reek, *Organometallics* **2010**, *29*, 2413.



Scheme 1.6

Due to the presence of only one NH in the urea moiety, the interaction between the two ligands during the formation of the complexes occurs in a different way from those mentioned before. The complexes formed, were finally investigated in rhodium-catalyzed hydroformilation reaction of styrene.

1.6 Oxazoline-containing chiral ligands

As it can be appreciated by the above overview, supramolecular bidentate ligands have been prepared, containing essentially phosphorus donor atoms.

Notwithstanding, nitrogen ligands have played important roles in asymmetric catalysis, and among the most widespread nitrogen ligands (e.g. amines, Schiff bases, oxazolines, etc.) bis(oxazolines) are the most successful ligands.

Starting from the first report by Wimmer in 1986 of the use of chiral oxazoline as ligands in asymmetric catalysis,[34] a wide range of ligands having one, two, or more oxazoline incorporating various heteroatoms, additional chiral motifs, and specific structural features have been used with great success in many asymmetric reactions, also because of the versatility of this ring, which is able to act as protector group, coordinating ligand, and activation moiety.

Oxazolines are five-membered cyclic and, although the oxazoline cycle was for the first time prepared in 1884,[35] it is starting from the 1970s that ligands containing oxazoline groups have been extensively applied.

Compounds containing chiral oxazolinic rings have become one of the most versatile and commonly used class of ligands for asymmetric catalysis.[36]

[34] H. Brunner, U. Obermann, P. Wimmer, *J. Organomet. Chem.* **1986**, *316*, C1.
[35] R. Andreasch, *Monatsh. Chem.* **1884**, *5*, 33.
[36] A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1; G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336; O. B. Sutcliffe, M. R. Bryce, *Tetrahedron: Asymmetry* **2003**, *14*, 2297.

In chiral oxazolines, the stereocenter lies close to the metal sphere in the catalytic species, since next to the nitrogen atom, thus having a direct influence on the stereochemical outcome of the reaction.
The ligands can be easily prepared from natural available aminoacids or synthetic aminoalcohols.

1.7 Bis(oxazolines)

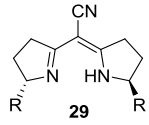
Bis(oxazolines) have developed into one of the most useful ligand class for asymmetric catalysis thanks to their ability to coordinate a large variety of metal ions as well as the excellent results in terms of activity and selectivity which can be attained in a number of enantioselective reactions.[37]
For bidentate ligands, of great importance is the concept of bite-angle, that is easily defined as the angle formed by two bonds existing between a metal center and two ligand atoms, therefore strongly dependent on the linker between the two donor groups.
It is well known that catalytic activity of the final catalyst is depending on the bite angle, so bidentate ligands can have a preference for a specific geometry and reactivity. Many pioneering studies have been undertaken in order to understand how exactly reactions are affected by the variation of the bite angle[38] but, although the progress in studying this concept and in the field of theoretical and computation chemistry, it is still not totally possible to predict the activity and selectivity of a catalytic system.
Nowadays, catalyst development still relies on a combination of intuition, laborious work and, quite often, in serendipity.

In 1986 Pfaltz and co-workers developed semicorrins **29**,[39] a new class of bidentate ligands having a rigid scaffold defined by the planar π-system and the two heterocycles. This feature makes them attractive as ligand for asymmetric metal catalysis.

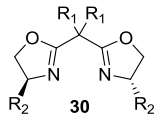
[37] G. C. Hargaden, P. J. Guiry, *Chem. Rev.* **2009**, *109*, 2505; R. Rasappan, D. Laventine, O. Reiser, *Coord. Chem. Rev.*, **2008,** 252, 702.
[38] S. Otsuka, J. *Organomet. Chem.* **1980**, *200*, 191; J. J. Low, W. A. Goddard, *J. Am. Chem. Soc.* **1984**, *106*, 6928; P. Hofmann, H. Heiss, G. Müller, Z. *Naturforsch. B,* **1987**, *42*, 395; P. Dierkes, P. W. N. M. van Leeuwen, J. *Chem. Soc. Dalton Trans.* **1999**, 1519; Z. Freixa, P. W. N. M. van Leeuwen, *Dalton Trans.* **2003**, 1890; R. Fazaeli, A. Ariafard, S. Jamshidi, E. S. Tabatabaie, K. A. Pishro, *J. Organomet. Chem.* **2007**, *692*, 3984; V. P. Ananikov, D. G. Musaev, K. Morokuma, *Eur. J. Inorg. Chem.* **2007**, 5390.
[39] H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem. Int. Ed.* **1986**, *25*, 1005.

These complexes showed a very high enantioselectivity in copper-catalyzed asymmetric cyclopropanation of olefins[40] and the cobalt-catalyzed conjugate addition of α,β-unsaturated esters and amides.[41]

The electron-rich vinylogous amidine group imparts an electron donating character to the ligands, reducing the electrophilicity of the metal center. For some reactivity, it is preferable to have a weak electron donating character or even a π-acceptor ligand.[42] In order to decrease this effect, in the early 90's neutral analogs of the semicorrins **29**, the (bis)oxazolines **30**, were independently developed by several groups.[43]



29



30

Bis(oxazolines), commonly called BOX, were then successfully applied with excellent results to a wide range of reactions including cyclopropanation of olefins and Diels-Alder reactions. Over the years, the popularity of these ligands rapidly increased due to two factors: the ease of synthesis and the catalytic activity.

Modification on the nature, size and flexibility of the linker and substituents on the two oxazolines, have led to the development of a plethora of BOX ligands which have been used in various reactions such as Diels-Alder, aziridination, cyclopropanation, allylic substitution, Mukayama, Michael, and many others.[44]

The bidentate bis(oxazoline) ligands of C_2-symmetry are constructed by two homochiral oxazoline rings connected to a central structure **A** (spacer) (Figure 1.2). In these ligands the coordination to the metal occurs through two nitrogen atoms. The degree of substitution of the two oxazoline rings and the metal employed in the catalyst construction are crucial factors governing the efficiency and the applicability of these ligands in asymmetric catalysis.

[40] A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339.
[41] U. Leutenegger, A. Madin, A. Pfaltz, *Angew. Chem. Int. Ed.* **1989**, *28*, 60; P. von Matt, A. Pfaltz, *Tetrahedron: Asymmetry* **1991**, *2*, 691.
[42] U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt, A. Pfaltz, *Tetrahedron* **1992**, *48*, 2143.
[43] D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc*. **1991**, *113*, 726; E. J. Corey, N. Imai, H-Y Zhang, *J. Am. Chem. Soc*. **1991**, *113*, 728.
[44] G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev*. **2006**, *106*, 3561; R. Rasappan, D. Laventine, O. Reiser, *Coord. Chem. Rev.* **2008**, *252*, 702.

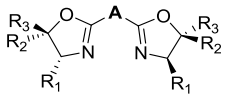
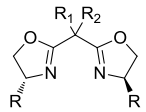


Figure 1.2

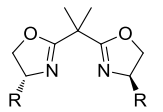
Here below, examples of some bis(oxazolines) employed in catalysis, will be list on the base of different typology of spacer **A**.

1.7.1 Bis(oxazoline) ligands separated by one carbon

(Bis)oxazolines with a carbon spacer between the two oxazolinic rings are the most frequently used, affording high selectivity in a wide range of metal-catalyzed reactions.

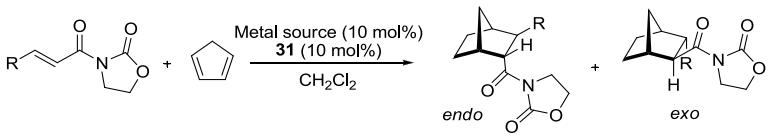


For instance, ligand **31** has found several applications in asymmetric transformations.



31 **a** R = Bn
b R = *iPr*
c R = Ph
d R = tBu
e R = indene

Sibi reported the application of **31c** in enantioselective Diels-Alder reaction, achieving 95% of ee (Scheme 1.7).[45]

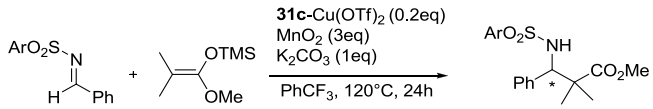


Scheme 1.7

[45] M. P. Sibi, S. Manyem, H. Palencia, *J. Am. Chem. Soc.* **2006**, *128*, 13660.

$Cu(OTf)_2$ complexes of **31d** were successfully applied by Yamazaki in the Friedel-Crafts reaction of a range of ethenetricarboxylates with various indoles in yields up to 87% and e.e.'s up to 95%.[46]

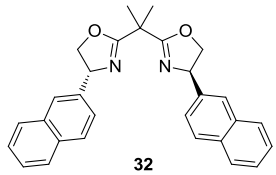
Ligands **31c** and **31e** were used for enantioselective Mannich-type reactions of imines in the presence of Lewis acids (Scheme 1.8).[47]



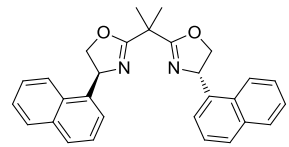
Scheme 1.8

In 1998 Desimoni developed ligand **32**, bearing a bulky 2-naphthyl groups in 4-position of the oxazolines, in an attempt to increase the selectivity of **31a**. The goal was achieved using different metal salts in the Lewis acid-catalyzed Diels-Alder reaction of cyclopentadiene and *N*-alkenoyl-oxazolidin-2-ones (Scheme 1.7).[48]

Ligand **33** was compared to **31** by Rutjes, who used the corresponding Cu(II)-complexes in Mukaiyama aldol reactions and Diels-Alder reactions. With ligand **33** the enantioselection achieved was higher than with the use of ligand **31a**, but significantly lower than with **31b**, the ligand *tert*-butyl-substituted.[49]



32

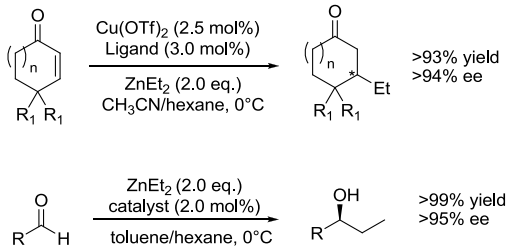


33

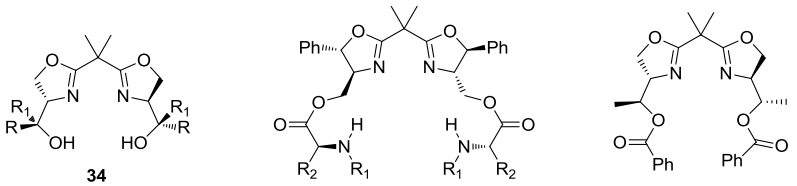
(Bis)oxazoline ligands which possess hydroxy groups at the stereogenic 4-position of the oxazoline rings, have been deeply studied by Reiser, who developed ligands **34**, suitable for both copper and zinc coordination.

[46] S. Yamazaki, Y. Iwata, *J. Org. Chem.* **2006**, *71*, 739.
[47] S. Nakamura, H. Sano, H. Nakashima, K. Kubo, N. Shibata, T. Toru, *Tetrahedron Lett.* **2007**, *48*, 5565.
[48] S. Crosignani, G. Desimoni, G. Faita, P. Righetti, *Tetrahedron* **1998**, *54*, 15721.
[49] H. L. van Lingen, J. K. W. van de Mortel, K. F. W. Hekking, F. L. van Delft, T. Sonke, F. P. J. T. Rutjes. *Eur. J. Org. Chem.* **2003**, 317.

The ligands were tested in copper(II)-catalyzed conjugate addition of diethylzinc to cyclic enones and in asymmetric addition of diethyl zinc to a range of aldehydes with good results (Scheme 1.9).[50]



Scheme 1.9



34

a R: Ph, R_1: H
b R: H, R_1: H
c R: Me, R_1: Me
d R: Ph, R_1: Ph

35

a R_1 = Cbz, R_2 = i-Pr
b R_1 = Boc, R_2 = Me
c R_1 = Ac, R_2 = Me
d R_1 = Ts, R_2 = Me

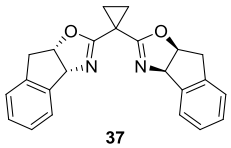
36

In 2003 Reiser investigated the use of ligands **34** and **35**, which possess secondary binding sites, in the copper(I)-catalyzed cyclopropanation.[51] In this work, the authors proposed that the hydrogen bond donor groups of the oxazolines 4-substituents are able to form hydrogen bonding with the substrate, controlling the direction of the attack.

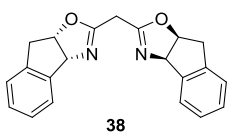
The dihydroxy bis(oxazoline) ligands **34a** and **36** were applied in the palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate using sodium hydride as the base by Aït-Haddou. Ligand **36** was the most selective, affording the product in 95% yield and 97% ee.[52]

Sibi applied the indene-derived ligand **37**, which contains a cyclopropyl linkage, in the 1,3-dipolar cycloaddition of nitrones and nitrile oxides with excellent results, obtaining enantioselectivities of 98% and 99%, respectively.[53]

[50] M. Schinneri, M. Seitz, A. Kaiser, O. Reiser, *Org. Lett.* **2001**, *3*, 4259.
[51] M. Schinnerl, C. Böhm, M. Seitz, O. Reiser, *Tetrahedron: Asymmetry* **2003**, *14*, 765.
[52] H. Aït-Haddou, O. Hoarau, D. Cramailére, F. Pezet, G-C Daran, G. G. A. Balavoinem *Chem.-Eur. J.* **2004**, *10*, 699.
[53] M. P. Sibi, M. L. Stanley, X. Nie, L. Venkatraman, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **2007**, *129*, 395.

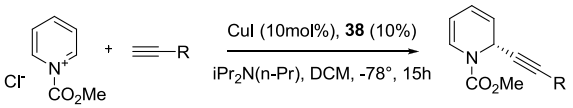


37



38

Ligand **38** was used by Ma in the copper-catalyzed enantioselective addition of different activated terminal alkynes to 1-acylpyridinium salts affording the final product in yield up to 81% and ee up to 99% (Scheme 1.10).[54]

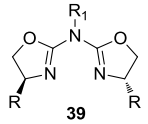


Scheme 1.10

1.7.2 Bis(oxazoline) ligands separated by heteroatoms

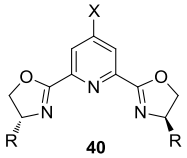
BOX with a range of bridges linking the chiral oxazoline rings have been developed and applied in metal-catalyzed asymmetric transformations. A peculiarity of this class is that they can be neutral, but also ionic, depending on the heteroatoms.

Reiser reported an interesting variant of ligands **30** where the central atom was replaced by a nitrogen atom, giving rise to the so called aza-bis(oxazolines).



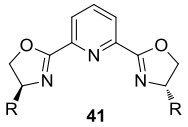
39

a R = *i*-Pr, R_1 = H
b R = *t*-Bu, R_1 = H
c R = *i*-Pr, R_1 = Me
d R = *t*-Bu, R_1 = Me
e R = *i*-Pr, R_1 = Bn



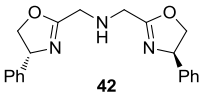
40

a R = iPr, X = NO_2
b R = iPr, X = H
c R = iPr, X = Me
d R = iPr, X = OMe
e R = Bn, X = NO_2



41

a R = Bn
b R = iPr
c R = Ph
d R = tBu
e R = adamantyl
f R = indene

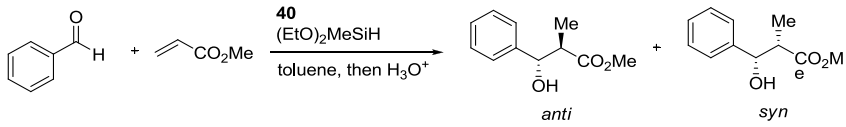


42

[54] Z. Sun, S. Yu, Z. Ding, D. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 9300.

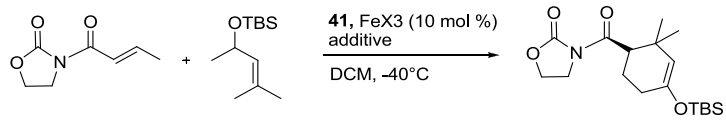
Ligands **39** were tested in palladium-catalyzed allylic alkylations and copper-catalyzed cyclopropanations affording very interesting results.[55] Afterward, Reiser proposed an interesting variant of these ligands, in which the aza-bis(oxazolines) were linked to a polimer. The novel bisbenzyl-substituted aza-bis(oxazoline) ligand proved to be very effective when immobilized to insoluble polymers.[56]

Nishiyama prepared ligands **40**, bearing a pyridine ring between the two oxazolines, and applied them in enantioselective aldol reductions (Scheme 1.11).[57] The reactions were complete within 30 min and in all cases afforded the aldol products in high yields (93-97%). The s*yn/anti* ratio obtained was between 15:85 and 12:88 and the highest ee% achieved 87%.



Scheme 1.11

Ligand **41**, belongs to the class of PyBOXs, as ligand **40,** was used in enantioselective Diels Alder reactions (Scheme 1.12).[58] The best result obtained was with $FeBr_3$ and $AgSbF_6$ in a 1:2 ratio, using **41c** as ligand that allowed the formation of the final product in 75% yield and 92% ee.



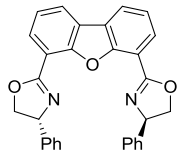
Scheme 1.12

Zhang used ligand **42** in Ru(II)-catalyzed transfer hydrogenation of aromatic ketones,[59] demonstrating the importance of the central NH, by comparing the excellent results achived with ligand **42** with the poor selectivity obtained with the use of the *N*-metylated analog.

A special type of heterotridentate bis(oxazolines), **43**, was recently reported by Willis, in which the two oxazoline rings are linked by a dibenzofuran moiety. The ligand was used in

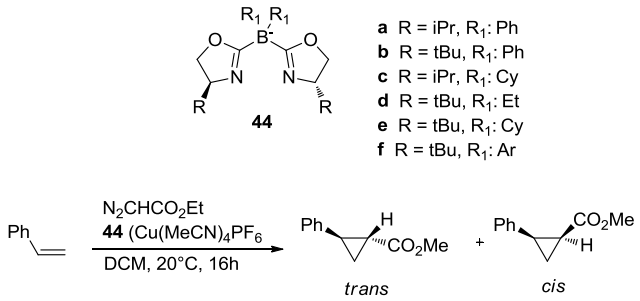
[55] M. Glos, O. Reiser, *Org. Lett.* **2000**, *2*, 2045.
[56] H. Werner, C. I. Herrerías, M. Glos, A. Gissibl, J. M. Fraile, I. Pérez, J. A. Mayoral, O. Reisera, Adv. Synth. Catal. **2006**, *348*, 125.
[57] T. Shiomi, J. Ito, Y. Yamamoto, H. Nishiyama, *Eur. J. Org. Chem* **2006**, 5594.
[58] H. Usuda, A. Kuramochi, M. Kanai, . Shibasaki, *Org, Lett.* **2004**, *6*, 4287.
[59] Y. Jiang, Q. Jiang, X. Zhang, *J. Am. Chem. Soc.* **1998**, *120*, 3817.

the Mannich reaction[60] and in the addition of nitrones to cyclopropanes[61] with excellent enantioselectivity in both cases.



43

A class of anaionic bis(oxazoline) ligands **44**, known as boraBOX, was instead used by Pfaltz in the enantioselective cyclopropanation of styrene (Scheme 1.13).[62] The boraBOX complexes showed similar reactivity of the corresponding BOX complexes.
Bulkier substituents at the boron atom induced higher enantioselectivities. Ligand **44e** provided the best results with a *cis/trans* ratio of 28:72.



Scheme 1.13

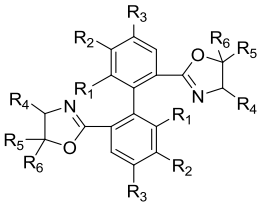
1.7.3 Bis(oxazoline) ligands separated by a stereo-axis

Ligands with biphenyl and binaphthyl backbone were the first stereoaxis-containing bis(oxazolines) to be employed in a wide range of asymmetric reactions.[63,64]

[60] Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociek-Ko¨hn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632.
[61] Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 16–5764.
[62] C. Mazet, S. Roseblade, V. Koehler, A. Pfaltz, *Org. Lett.* **2006**, *8*, 1879.
[63] Y. Uozumi, H. Kyota, E. Kishi, K. Kitayama, T. Hayashi, *Tetrahedron*: *Asymmetry* **1996**, *7*, 1603; T. G. Gant, M. C. Noe, E. J. Corey, *Tetrahedron Lett.* **1995**, *36*, 8745; M. B. Andrus, D. Asgari, J. A. Sclafani, *J. Org. Chem.* **1997**, *62*, 9365.
[64] Y. Uozumi, K. Kato, T. Hayashi, *J. Am. Chem. Soc.* **1997**, *119*, 5063; Y. Uozumi, K. Kato, T. Hayashi, *J. Org. Chem.* **1998**, *63*, 5071.

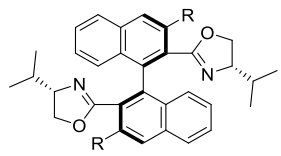
Rippert prepared a numerous library of bis(phenyl) analogs **45** and investigated their characteristics in the copper(I)-catalyzed cyclopropanation of styrene with ethyl diazoacetate finding out an enantioselectivity dependence on the steric hindrance at the 5-position of the oxazoline ring. [65]

A binaphthyl skeleton was used by Hayashi to prepare ligands **46** for applications to Pd(II)-catalyzed Wacker-type cyclizations.[66]



45

a R_1 = Me, OMe, Br
b R_2 = H, OMe
c R_3 = H, OMe, Br
d R_4 = Et, i-Pr, Ph, Me, t-Bu
e R_5,R_6 = H, Ph

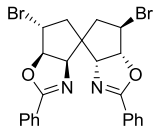


46

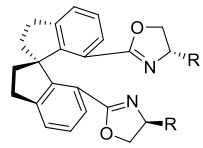
a R = CO_2Me
b R = $SiMe_3$
c R = $CONMe_2$
d R = CHO
e R = I

An interesting class of bis(oxazolines), the chiral spiro ligand **47**, was introduced by Sasai in 2004 and employed in a range of asymmetric reactions,[67] and lateron refined by Zhou.

In this contest, Zhou reported also the synthesis of ligands **48** and their application to the catalytic asymmetric N-H insertion of amines with diazoesters,[68] and to the enantioselective insertion of carbenoids into the O-H bonds of phenols,[69] (Scheme 1.14), describing very recently the intramolecular phenolic O-H bond insertion.[70] (Scheme 1.15)



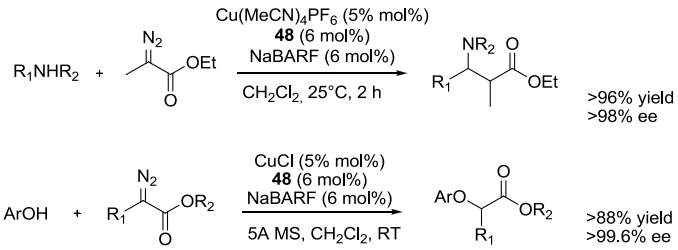
47



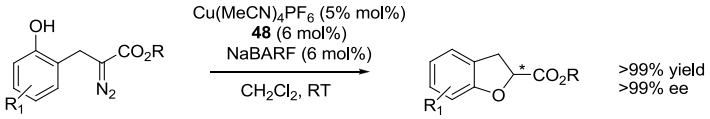
48

a R = *i*-Pr
b R = Ph
c R = Bn
d R = *t*-Bu
e R = Me
f R = H

[65] A. J. Rippert, *Helv. Chim. Acta* **1998**, *81*, 676.
[66] Y. Uozumi, H. Kyota, K. Kato, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **1999**, *64*, 1620.
[67] T. Kato, K. Marubayashi, S. Takizawa, H. Sasai, *Tetrahedron: Asymmetry* **2004**, *15*, 3693.
[68] B. Liu, S-F. Zhu, C. Chen, Q-L. Zhou, *J. Am. Chem. Soc.* **2007**, *129*, 5834; S-F. Zhu, B. Xu, G-P. Wang, Q-L. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 436.
[69] C. Chen, S-F. Zhu, B. Liu, L-X. Wang, Q-L. Zhou, *J. Am. Chem. Soc.* **2007**, *129*, 12616.
[70] X-G. Song, S-F. Zhu, X-L. Xie, Q-L. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 2555.

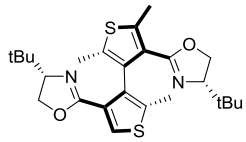


Scheme 1.14



Scheme 1.15

Cu(I)-catalyzed cyclopropanation of styrene with ligand **49**, characterized by the 3,3'-bithiophene backbone, was able to give the final product in 81%, 67% of ee, and with a *trans/cis* ratio of 67:33.[71] (Scheme 1.13)



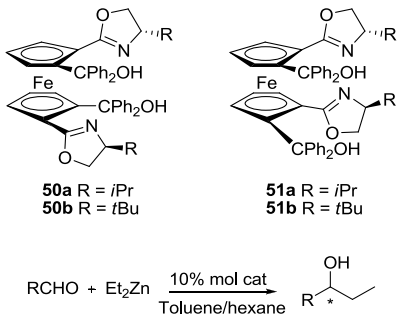
49

1.7.4 Bis(oxazoline) ligands separated by a stereo-plane

A class of bis(oxazolines) that is worth mentioning consists in the ferrocenyl derivatives. In these ligands a stereo-plane replaces the usual stereocenters, in order to optimize the enantioselectivity of the tested reactions.

Ikeda prepared several tetrasubstituted oxazolinylferrocenes **50** and **51**, reaching yields up to 97% and ee up to 93% in asymmetric alkylation of benzaldehyde with diethylzinc (Scheme 1.16).[72]

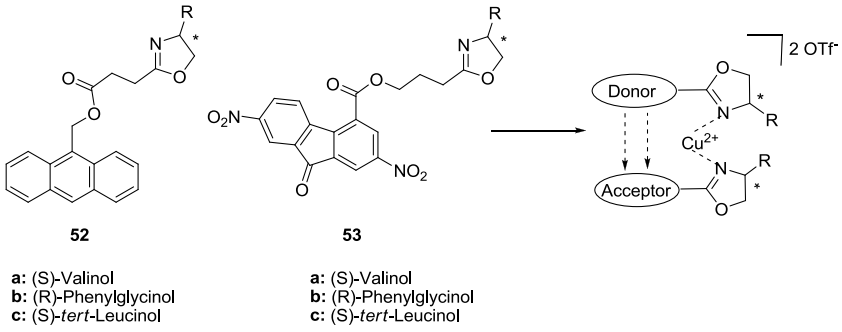
[71] M. Benaglia, T. Benincori, P. Mussini, T. Pilati, S. Rizzo, F. Sannicolò, *J. Org. Chem.* **2005**, *70*, 7488.
[72] W. B. Zhang, H. Yoshinaga, Y. Imai, T. Kida, Y. Nakatsuji, I. Ikeda, *Synlett* **2000**, *10*, 1512; Y. Imai, S. Matsuo, W. B. Zhang, Y. Nakatsuji, I. Ikeda, *Synlett* **2000**, *2*, 239.



Scheme 1.16

1.7.5 Bis(oxazoline) ligands formed by supramolecular interaction

In 2008, Schultz published, to the best of our knowledge, the only example reported in literature for supramolecular bis(oxazoline) ligands formed *via* charge transfer interaction of two monodentate oxazolines. She reported the synthesis of mono(oxazoline) ligands from three different amino alcohols and bearing either an electron-rich anthracene group **52** or an electron-poor trinitrofluorenone substituent **53**. In the presence of copper triflate as pre-catalyst, all the ligand combinations were tested, proving to give rise to active catalysts for the Diels–Alder reaction between cyclopentadiene and 3-but-2-enoyl-oxazolidin-2-one, albeit only poorly enantioselective (Scheme 1.17).[73]



Scheme 1.17

However, the best results in terms of enantioselectivity were obtained with the homocomplex formed from two electron-poor trinitrofluorenone oxazolines (therefore not able to form a supramolecular catalyst), for either the *endo* or the *exo* product.

[73] O. Chuzel, C. Magnier-Bouvier, E. Schultz, *Tetrahedron: Asymmetry* **2008**, *19*, 1010.

1.8 Development of a new class of supramolecular bidentate nitrogen ligands.

As discussed in the introduction, the concept of self-assembly of ligands through hydrogen bonding for combinatorial homogeneous catalysis was recently introduced, and several powerful supramolecular ligands were described with outstanding reactivity and selectivity. However, this methodology developed has been exclusively confined to the use of phosphorus ligands.[74]

Therefore, we decided to extend this concept to nitrogen ligands for the synthesis of the first supramolecular bisoxazoline ligands, that we called SupraBox (Figure 1.3).

In our approach, a covalent linker is replaced by a hydrogen-bond interaction between two urea moieties that are connected to the oxazoline rings via different spacers. Transition metal complexes with SupraBox were formed and applied to asymmetric transformations.

In particular, the Zn(II)-complexes were used as catalysts for the Friedel-Crafts alkylation of the indole with fuctionalized alkenes, while the Cu(II)-complexes for kinetic resolution and desymmetrization of 1,2-diol.[75]

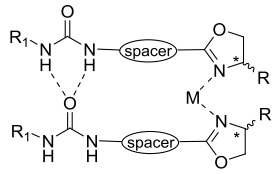


Figure 1.3

1.8.1 Synthesis of the ligands

In general terms a class of ligands suitable for a combinatorial exploitation should be accessed in a limited number of steps, through a highly modular synthesis which allows the creation of a wide diversity from a limited number of building blocks.

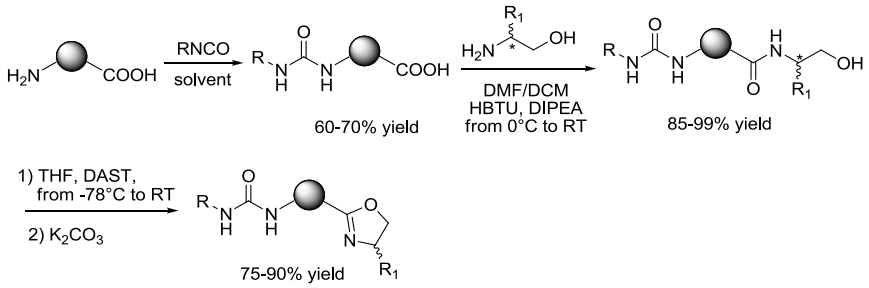
The SupraBox ligands possess three possible tunable sites:

- the oxazoline moiety,
- the spacer,
- the urea substituents,

[74] L. K. Knight, Z. Freixa, P. van Leeuwen, J. N. H. Reek, *Organometallics* **2006**, *25*, 954; A. J. Sandee, A. M. van der Burg, J. N. H. Reek, *Chem. Commun.* **2007**, 864; J. Meeuwissen, M. Kuil, A. M. van der Burg, A. J. Sandee, J. N. H. Reek, *Chem. Eur. J.* **2009**, *15*, 10272.

[75] M. Durini, E. Russotto, L. Pignataro, U. Piarulli, O. Reiser, *Eur. J. Org. Chem.* **2012**, 5451.

which can be coupled in three straightforward synthetic steps involving only two chromatographic purifications (Scheme 1.18).

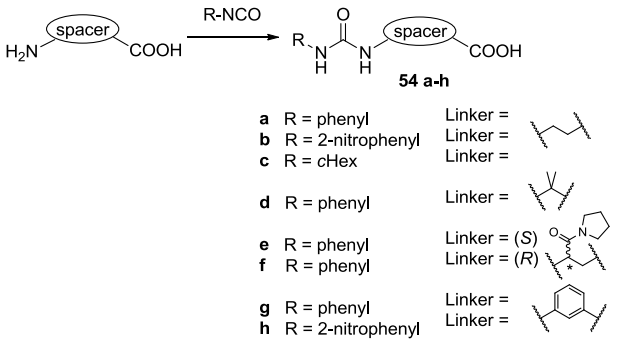


Scheme 1.18

Three different isocyanates (phenyl, cyclohexyl and 2-nitrophenyl isocyanate) were included in the screening to vary the H-bond forming properties of the ligands.

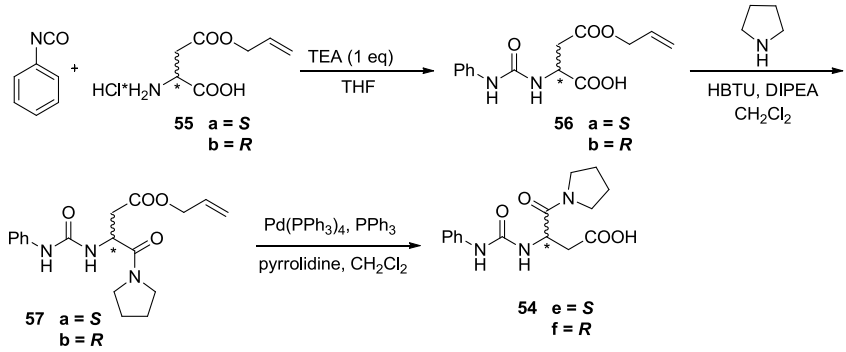
The formation of the urea is probably the limiting step in terms of total yield of the synthesis, the main problem being due to the low solubility of the different amino acids used in the reaction. In general THF proved to be the a good solvent even if the solubility of products was not optimal. In one case the almost total insolubility of the 2-amino-isobutyric acid necessitated the use of a 2M NaOH solution as solvent, anyway leading low yield.

Four different linkers, namely β-alanine, 2-amino-isobutyric acid, L- and D-aspartic acid α-pyrrolidinamide and 3-aminobenzoic acid, were used to impart different conformational rigidity to the ligands and hence influence the global conformation of the complexes (Scheme 1.19).



Scheme 1.19

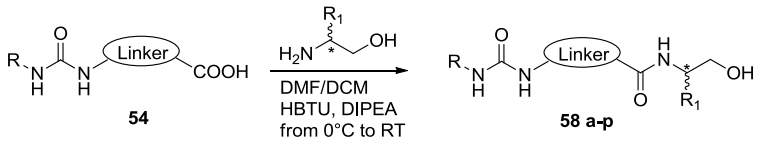
Achiral linkers were readily available commercial products, whereas the chiral linker was synthesized *ad hoc* starting from aspartic acid (Scheme 1.20). In particular, the presence of stereocenters at the α-position of carboxylic groups (and hence of oxazolines) were deemed dangerous in terms of the stereo-integrity of the final ligand. Oxazolines in fact are known to be susceptible of epimerization during the coupling of the starting carboxylic acid with the amino alcohols and the subsequent cyclization. On the other hand commercial enantiopure β^3-homo amino acids are very expensive and, despite several published synthetic protocols, suffer from difficult availability in multigram quantities.



Scheme 1.20

Coupling of the amino alcohols gave no particular problems using standard procedures, but chromatographic purification of the resulting amides was complicated by the use of DIPEA. An acidic work-up would be theoretically sufficient to remove the base, however the tendency of the product to be soluble in aqueous phases made this procedure not recommended.

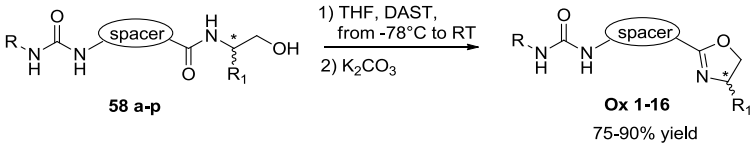
Different substituents on the oxazoline ring lead obviously to a different chemical environment around the catalyst metal and consequently different levels of steric hindrance can modify the selectivity of the catalyst. Due to the synthetic strategy the stereochemistry and the nature of the substituent is related to the starting amino alcohol (Scheme 1.21).



a Acid = **54a**, R_1 = (*R*)-Et
b Acid = **54a**, R_1 = (*S*)-Bn
c Acid = **54a**, R_1 = (*S*)-*i*Pr
d Acid = **54a**, R_1 = (*R*)-Ph
e Acid = **54b**, R_1 = (*S*)-Bn
f Acid = **54c**, R_1 = (*S*)-*i*Pr
g Acid = **54d**, R_1 = (*S*)-*i*Pr
h Acid = **54d**, R_1 = (*R*)-Et
i Acid = **54e**, R_1 = (*S*)-*i*Pr
j Acid = **54f**, R_1 = (*S*)-*i*Pr
k Acid = **54g**, R_1 = (R)-Et
l Acid = **54g**, R_1 = (S)-Bn
m Acid = **54g**, R_1 = (*S*)-*i*Pr
n Acid = **54g**, R_1 = (*S*)-*t*Bu
o Acid = **54g**, R_1 = (*R*)-Ph
p Acid = **54h**, R_1 = (*S*)-*i*Pr

Scheme 1.21

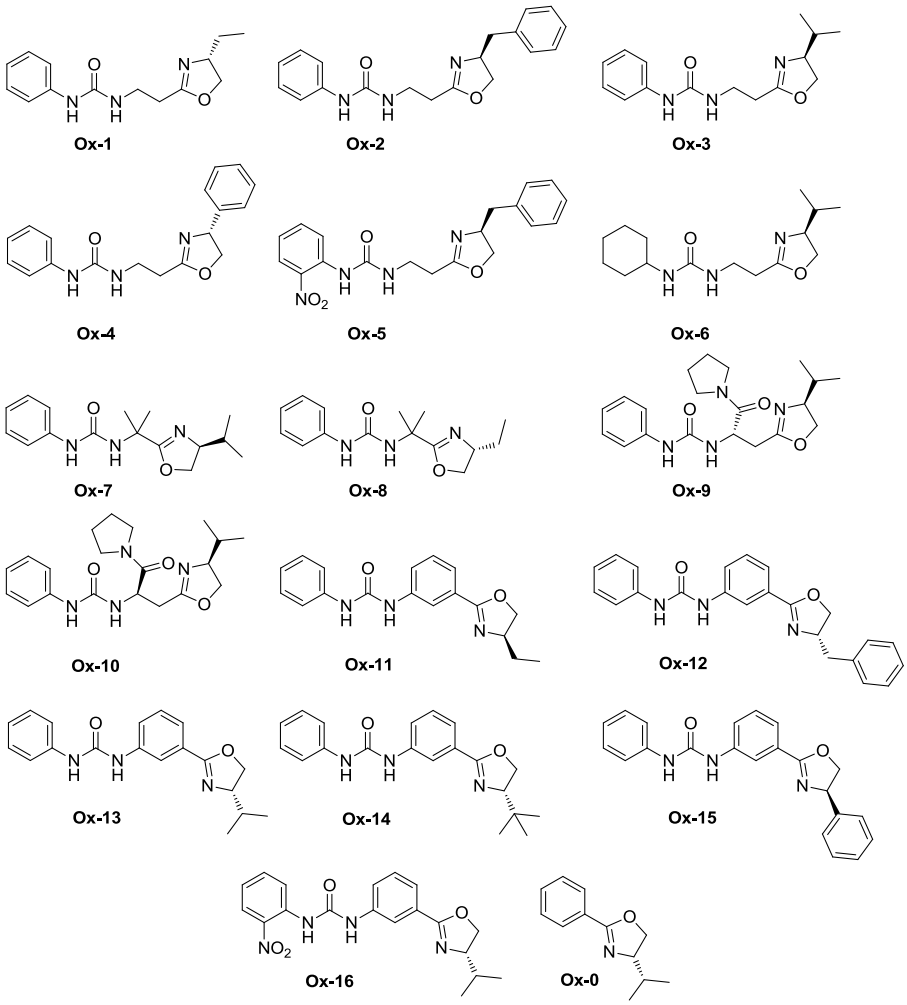
Cyclization reactions to give the oxazoline ring were carried out using diethylaminosulfur trifluoride (DAST) at -78°C. Due to the presence in the molecule of other nucleophilic oxygen atoms, an excess of DAST (2.2 equiv.) was necessary to obtain the cyclized product in good yieldsc(Scheme 1.22).



Scheme 1.22

Due to the modularity of the synthesis, a small library of 16 ligands **Ox 1-16** was prepared for testing them in metal complex-catalyzed transformations.

In addition, one monooxazoline **Ox-0**, devoid of the functionality capable of hydrogen bonds, was added to validate the importance of the supramolecular interactions.



1.8.2 Formation of the metal complexes and complexation studies

Before screening the library in catalytic applications we decided to investigate the formation of transition metal complexes of our ligands.

Bis(oxazolines) have been developed into one of the most useful ligand classes due to their ability to coordinate different metals and also to impart specific coordination geometries to these metal ions.

The resulting chiral complexes display a C_2-axis, a feature that has proven most beneficial in designing asymmetric processes due, in general, to the reduction of possible transition states caused by the equivalency of structures upon rotation by 180° (Figure 1.4).

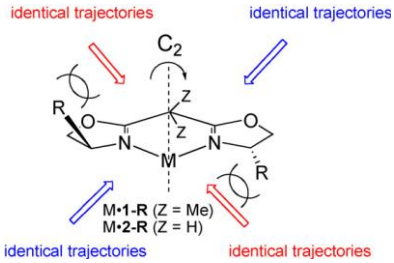


Figure 1.4

In the majority of bis(oxazoline) complexes, the metal is a four to six coordinated species; therefore, besides the two coordination sites occupied by the bidentate ligand, substrates, solvent molecules or counter anions, occupied the other available sites. The geometry of the complexes is a result of many factors and affects the outcome of a given reaction.

Copper is known to be one of the metals with more coordination geometries, forming tri- tetra- penta- and hexacoordinate complexes.

Tricoordinated complexes are almost exclusively prerogative of Cu(I), and in particular of copper(I)-carbene complexes as intermediates in cyclopropanations of alkenes with diazoacetates.[76]

The two main geometries possible for tetracoordinated bis(oxazoline) complexes are square-planar and tetrahedral. These are indeed widely found with varying degrees of distortion.

Zinc(II), nickel(II) and iron(II) chloride complexes have proven to form distorted tetrahedral complexes, meanwhile with copper(II) chloride, coordinations are considerably more distorted towards a square-planar geometry.

Quite obviously, the chloride ligands, when present, orient themselves away from the ligand quadrants blocked by the sterically demanding substituent and in general it is possible to say that the degree of distortion from the ideal tetrahedral geometry increases with the steric bulk of the oxazoline substitution (Scheme 1.23-A).[77]

A similar trend is present for square-planar Cu(II)-complexes, which is a marked preferred geometry for hydroxyl- or carbonyl-containing ligands (Scheme 1.23-B).[78]

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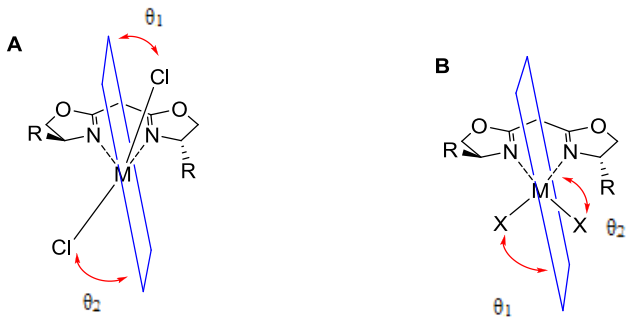
[76] R. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005; R. E. Lowenthal, S. Masamune, *Tetrahedron Lett.* **1991**, *32*, 7373; D. A. Evans, K. A.Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726.

[77] J. Thorhauge, M. Roberson, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2002**, *8*, 1888; D. A. Evans, S. J. Miller, T. v. M. P. Lectka, *J. Am. Chem. Soc.* **1999**, *121*, 7559; R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Org. Lett.* **2006**, *8*, 6099.

[78] D. A. Evans, G. S. Peterson, J. S. Johnson, D. M. Barnes, K. R. Campos, K. A. Woerpel, *J. Org. Chem.* **1998**, *63*, 4541; D. A. Evans, T. Rovis, J. S. Johnson, *Pure Appl. Chem.* **1999**, *71*, 1407; D. A. Evans, T. Rovis, M. C.



Scheme 1.23

Hexacoordinated complexes are almost absent with bis(oxazoline) ligands, meanwhile pentacoordinated are more diffused.

We focused our attention on copper- and zinc-complexes.

The copper(II)-complex of ligand **Ox-3** was obtained treating the ligand with $CuCl_2$ in CH_2Cl_2, followed by recrystallization from CH_2Cl_2/hexanes. Its molecular composition was assessed by ESI-MS spectrometry and revealed one principal peak at *m/z* 613.3, corresponding to a copper atom coordinated to two molecules of ligand $[Cu(Ox\text{-}3)_2]^+$ (Figure 1.5).

The reduction of Cu^{2+} to Cu^+ has been already reported to occur using ESI as ionization source, in which the electron counterflow between the counterelectrode and the capillary causes an increase of the Cu(I) species.[79] In particular, the reduction of Cu(II) species can be induced by direct electron capture in the atmospheric pressure region of the source, before the entrance in the glass capillary.

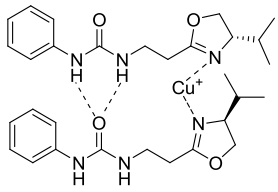
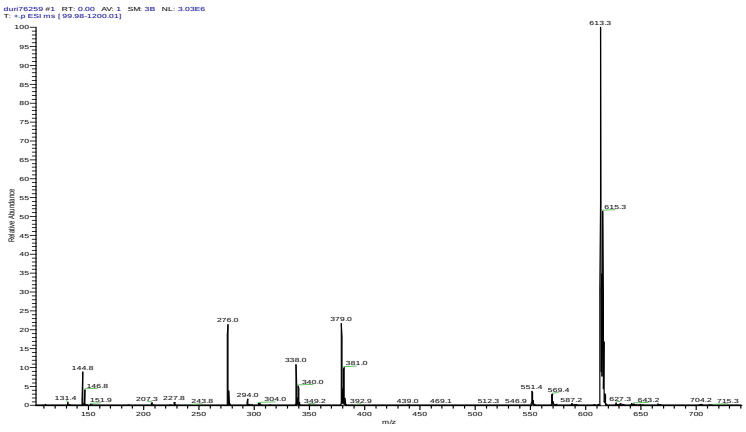


Figure 1.5

Kozlowski, C. W. Downey, J. S. Tedrow, *J. Am. Chem. Soc.* **2000**, *122*, 9134; D. A. Evans, T. Rovis, M. C. Kozlowski, J. S. Tedrow, *J. Am. Chem. Soc.* **1999**, *121*, 1994.

[79] Lavanant, H.; Virelizier, H.; Hoppilliard, Y. J. *J Am Soc Mass Spectrom* **1998**, *9*, 1217.



Another interesting technique that allowed us to determine the formation of the desired complex, was the Yoe–Jones analysis.

In general, when we deal with reactions based on the coordination of ligands to a metal source to give a complex M_xL_n, absorption spectroscopy is a powerful tool for exploring the complexation.

Two general approaches to study the composition of complexes are typically used:

- Method of Continuous Variations (Job's Method)

In this method, the metal cation and ligand solutions with identical concentrations are mixed in different amounts such that the total volume of the mixture solutions and the total moles of reactants in each mixture is constant. This procedure causes the mole ratio of reactants to be varied across the set of mixture solutions. The absorbance of each solution is then measured and plotted versus the volume fraction of one of the reactants (M or L).

- Mole-Ratio Method (Yoe-Jones Method)

In this method, a series of solutions is prepared in which the concentration of one reactant is held constant while that of the other is varied. The absorbance of each solution is measured and plotted versus the mole ratio of the reactants. Assuming the complex absorbs more than the reactants, this plot will produce an increasing absorbance up to the combining ratio. At this point, further addition of reactant will produce less increase in absorbance. Thus a break in the slope of the curve occurs at the mole ratio corresponding to the combining ratio of the complex.

Both techniques provide interesting information about the coordination processes of the ligand to metal, and also about the global stability constant of complexes.[80]

For our complexation studies, we focus the attention on the Yoe-Jones method.

In a typical representation, the analytical signal increases with the ligand mole ratio until a maximum is reached; from this point the analytical signal is maintained constant. The maximum value of the curve corresponds to the maximum formation of the complex and it indicates the stoichiometry of the complex .

The curvature of the line obtained depends on the stability of the complex; the more stable it is, the closer the lateral segments of the experimental curve approach a straight line, and it means that the formation of the complex is practically total. For weak complexes, the experimental curve does not present any straight segments.

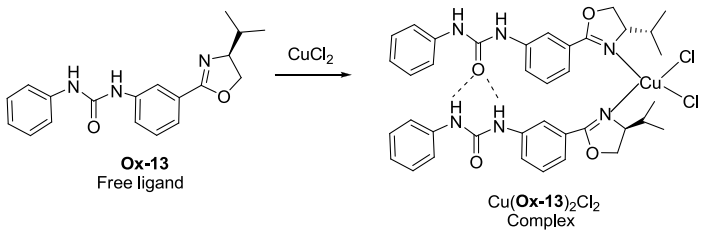
In our experiments, we chose **Ox-13** as ligand and we measured the absorbance (λ_{MAX} = 741 nm) as a function of the ligand/metal ratio, and a linear increase up to two equivalents of ligands added was observed, suggesting the presence of only one species ascribable to one copper coordinated to two molecule of ligands.

The procedure required multiple and constant additions to $CuCl_2$ in dichloromethane of a stock solution of the ligand, directly in the glass cuvette used for the analysis.

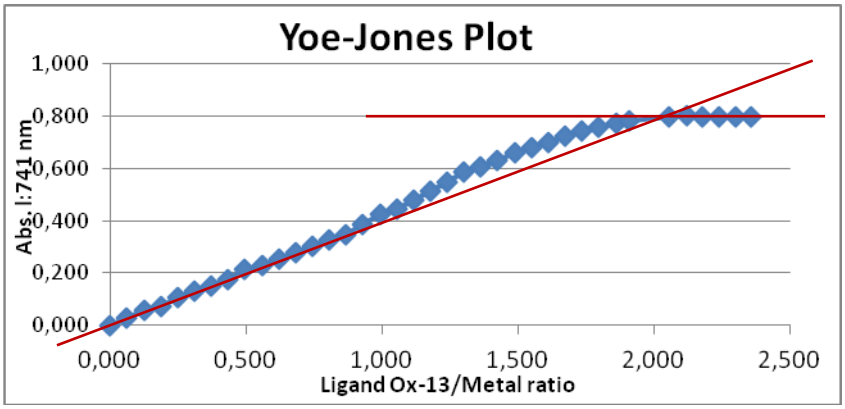
Initially the solution was clear and colorless with $CuCl_2$ insoluble as residue. The solution started to become greener and greener at each addition, as soon as the first portion of ligand was added. It is necessary to stress that, only when the amount of ligand added reached 2 equivalents, the insoluble residue of $CuCl_2$ totally disappeared.

According to this type of analysis, the stochiometry of the complex is estimated from the point in which the curve changes its slope.

All the observations led us to assumed the unique formation of the desired product Cu(**Ox-13**)$_2$Cl$_2$ (Scheme 1.24).

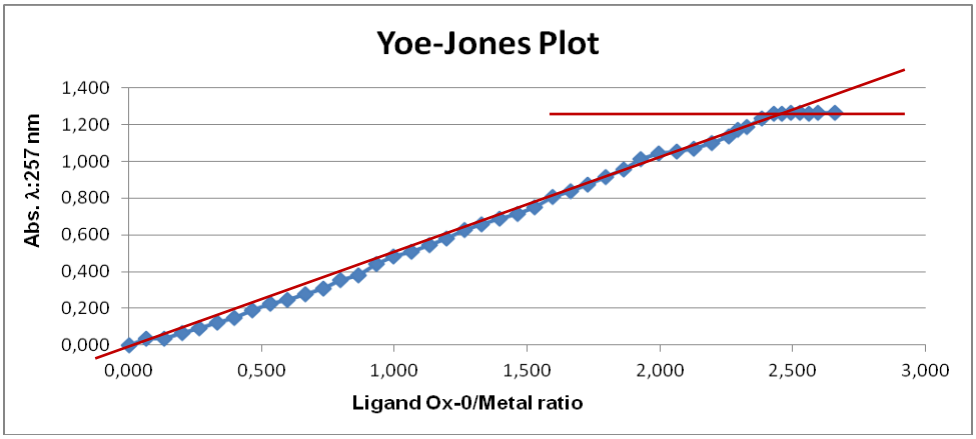


[80] E. J. Olson, P. Bühlmann, *J. Org. Chem.* **2011**, *76*, 8406.



Scheme 1.24

Besides, we decided to explore the complexation of ligand **Ox-0**, the oxazoline devoid of the urea group. As for **Ox-13**, we measured once again the absorbance (λ_{MAX} = 757 nm) as a function of the ligand/metal ratio.



Scheme 1.25

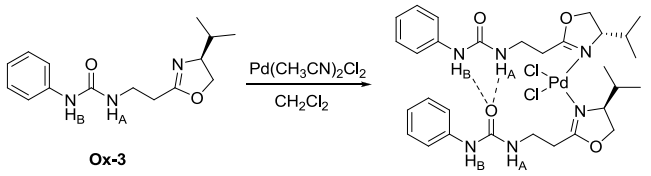
Again, a linear increase for each portion of ligand added was observed but, this time, the absorbance increased until the amount of ligand added was 2.5 equivalents, and still a slight portion of solid $CuCl_2$ remained undissolved even after that was reached a constant value of absorbance (Scheme 1.25).

Our explanation is that probably a series of equilibria occur and the formation of the final complex is a bit arduous to obtain; whereas the presence of the urea moiety in **Ox-13**, lead most likely to the immediately formation of a supramolecular bidentate ligands, hence

helping the formation of the desired complex and avoiding the possibility of the inconvenient mixture of equilibria. Moreover, the deviation from linearity could depend on the stability of the complex with respect to ligand dissociation:[81] the more stable the complex is, the closer the experimental curve approaches a straight line.

The paramagnetism of Cu(II) hampers the use of NMR spectroscopy for the characterization of the complex. Thus, palladium was chosen.

Bis(acetonitrile)dichloropalladium(II) and two equivalents of ligand **Ox-3** were stirred in dichloromethane and the complex [Pd(**Ox-3**)$_2$Cl$_2$] was isolated by precipitation with hexanes (Scheme 1.26).



Scheme 1.26

The formation of the supramolecular bidentate species was then studied by ^{1}H-NMR.

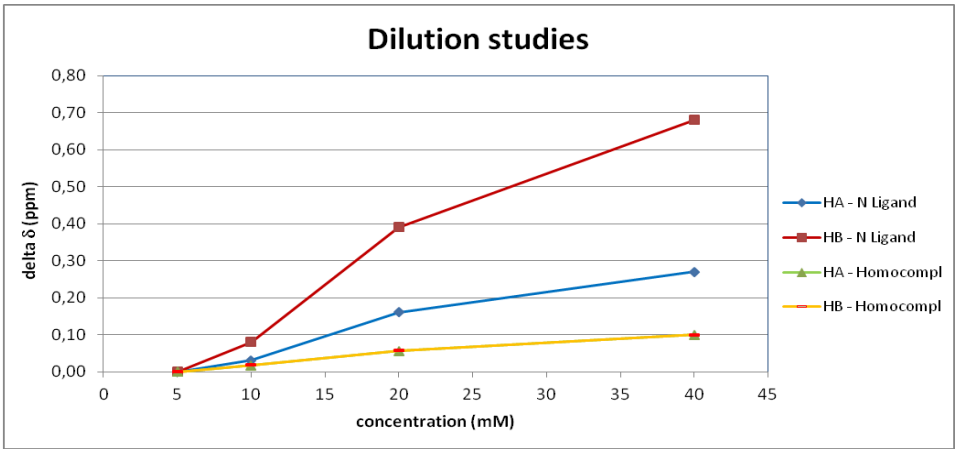
The attention was mainly focused on NH protons, the more representative signals. While coordination of the oxazolines to the metal ion is quite certain, coordination of two ligands on the same atom and moreover an interaction between them is far from obvious. So, a study of the chemical shifts of protons, which should give rise to H-bonding, should provide important information.

The hydrogen bonding status of the NH protons for both the free ligand and the Pd(II)-complex was then studied by ^{1}H-NMR spectroscopy. In particular, the correlation between the variation of the chemical shift of the NH signals and the variation of the concentration was considered for both the ligand and the complex, and finally reported in the plot here below. This trend, if present, is important for showing a possible chemically different behavior of the NHs.

[81] C. D. Chriswell, A. A. Schilt, *Analytical Chem.* **1975**, *9*, 1623.

(*S*) Ox-3	NHA		NHB	
concentration (mM)	δ A	Δδ A	δ B	Δδ B
5	5,62	**0,00**	6,80	**0,00**
10	5,65	**0,03**	6,88	**0,08**
20	5,78	**0,16**	7,19	**0,39**
40	5,89	**0,27**	7,48	**0,68**

Homocomplex	NHA		NHB	
concentration (mM)	δ A	Δδ A	δ B	Δδ B
5	5,74	**0,00**	7,03	**0,00**
10	5,76	**0,02**	7,05	**0,02**
20	5,80	**0,06**	7,09	**0,06**
40	5,84	**0,10**	7,13	**0,10**



The results clearly show that the ligand alone behaves differently from when it is in a complex.

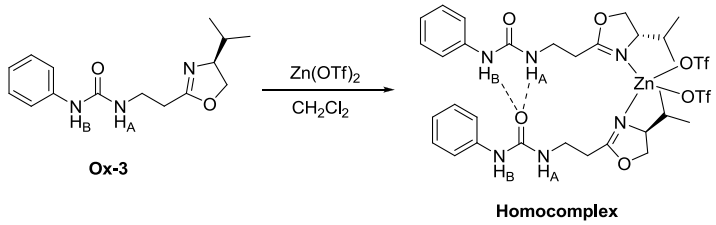
The downfield shift of the chemical shifts of the two NH protons of the complex is not depending on the concentration as much as those of the free ligands. NH_A and NH_B proton signals of the homocomplex can better be considered fairly independent from the concentration.

What now seems curious is the lack of different sets of signals. Since one ligand acts as donor and the other as acceptor, two different sets of chemical shift should be present. So, we decided to investigate the behavior of the complex as a function of temperature and we found out that at temperature lower than 268K two signals appeared.

This experiment, commonly used to differentiate between random-coil peptides and peptides in hydrogen bonded conformations, together with previous observations, indicates that the two ligands coordinated to the metal atom interact intramolecularly *via* hydrogen bonds.

In order to verify complexation with zinc, only preliminary studies were done and they confirmed the formation of a supramolecular bidentate complex.

Ligand **Ox-3** was chosen and reacted with Zinc(II)trifluoromethanesulfonate in dichloromethane. The resulting [Zn(**Ox-3**)$_2$(OTf)$_2$] complex was isolated by precipitation with hexanes (Scheme 1.27).



Ox-3 **Homocomplex**

Scheme 1.27

The downfiled shift of the urea protons in the ^{1}H-NMR spectrum is consistent with the formation of the supramolecular bidentate complex: NH$_A$ signal for **Ox-3** is at 5.62 ppm, while in the complex at 6.04ppm. On the other hand, NH$_B$ signal for **Ox-3** is at 6.80 ppm, while in the complex at 7.05ppm.

This trend, if present, is important to show a possible chemically different behavior of the NHs, that in our case would indicate the presence of hydrogen bonding.

1.8.3 Catalytic applications

1.8.3.1 Friedel-Crafts alkylation of indoles

Lewis acid-catalyzed Friedel-Crafts alkylation reaction is a powerful carbon-carbon bond-forming process in organic chemistry. The asymmetric version of this reaction can provide a very useful approach to the enantiomerically enriched alkylated arene products.

Examples of this reaction in literature mainly foresee the use of covalent bis(oxazolines) as ligands. Optically active indole derivatives have attracted significant attention in organic synthesis because they are important building blocks in a variety of interesting natural products and potential medicinal agents.[82]

The asymmetric Friedel-Crafts reaction is one of the most powerful carbon-carbon bond-forming reactions in synthetic organic chemistry; for this reason, Friedel–Crafts alkylation of indoles[83] has shown promise as a synthetic methodology towards functionalized indoles.

α,β-unsaturated carbonyl compounds are very suitable substrates for this reactions and they have been overwhelmingly investigated over the last years.

On the other hand, the use of nitroalkenes is more recent but the easy transformation of the nitro group into a range of different functionalities makes their use even more attractive.

Nitroalkenes are very active Michael acceptors,[84] and the products of the alkylations of indoles with nitroalkenes can be applied to the synthesis of many biologically active compounds.

In 2001, Jørgensen reported the first example of this reaction using a C_2-symmetric chiral bis(oxazolines)-copper(II) complex as catalyst.[85] Subsequently, other authors employed bis(oxazolines)-complexes to promote the reactions and, later on, Reiser examined the oxazoline/metal ratio influence on the enantioselectivity.[86]

Reactions with α,β-unsaturated carbonyl compounds, such as alkylidene malonate, are almost completely confined to the use of Cu(II)–bis(oxazolines) complexes.

However, recently, the knowledge that these substrates are able to chelate a series of Lewis acids in many asymmetric reactions,[87] has lead to the employment of different Lewis acids in the reactions. In the case of nitroalkenes, Zn(II)-complexes have mainly been used as catalysts reported in leterature.[88]

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[82] J. P. Kutney, *The Total Synthesis of Natural Products: The Synthesis of Indole Alkaloids* (Ed.: J. ApSimon), Wiley-Interscience, New York, **1977**; A.-u. -Rahman, A. Basha, *Indole Alkaloids*, Harwood Academic, Chichester, **1998**; D. J. Faulkner, Nat. Prod. Rep. 2002, 19, 1.

[83] M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 550; D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt, R. S. Xu, *J. Am. Chem. Soc*. **2007**, *129*, 10029; T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903.

[84] O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877.

[85] W. Zhang, T. Hansen, K. A. Jørgensen, *Chem. Commun.* **2001**, 347.

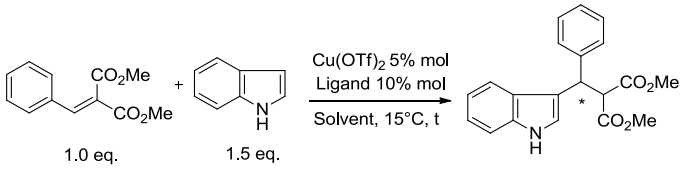
[86] R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Org. Lett.* **2006**, *8*, 6099; A. Schtz, R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Chem. Eur. J*. **2008**, *14*, 7259.

[87] J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030, D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey, J. S. Tedrow, *J. Am. Chem. Soc.* **2000**, *122*, 9134.

[88] S-F. Lu, D-M Du, J. Xu, *Org. Lett.* **2006**, *8*, 2115; Y-X. Jia, S-F. Zhu, Y. Yang, Q-L. Zhou, *J. Org. Chem.* **2006**, *71*, 75; H. Liu, D-M. Du, *Eur. J. Org. Chem.* **2010**, 2121.

In view of the above considerations, we decided to screen some of our ligands in the Friedel-Crafts alkylation of indole.

We started with benzylidenemalonate. The reactions were carried out in dichloromethane using one equivalent of alkylidene malonate, 2 equivalents of indole, 5 mol% of $Cu(OTf)_2$ and 10 mol% of the chosen ligand (Table 1.1).



1.0 eq. 1.5 eq.

59 **60** **61**

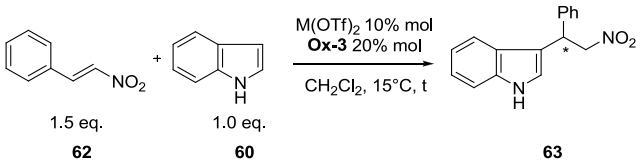
Entry	Ligand	Yield[a] (%)
1	**none**	30
2	**Ox-0**	10
3	**Ox-2**	13
4	**Ox-3**	34
5	**Ox-4**	n.r.
6	**Ox-6**	21
7	**Ox-7**	26
8	**Ox-13**	63
9	**Ox-15**	n.r.
10	**Ox-16**	12

[a] Isolated by flash chromatography. Eluent: EDP/AcOEt 5:1
enantiomerc excess determined by HPLC: Column Chiracel OD-H, Hex/IPA 88:12, flow 0,8 mL/min
Table 1.1

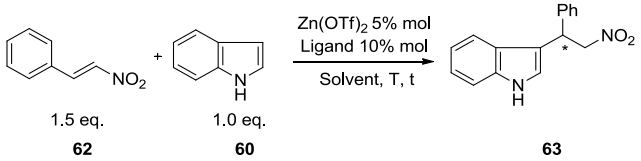
First of all, the reaction was catalyzed by the precatalyst $Cu(OTf)_2$, affording the final product in 30% yield after 3 days; while the formation of the catalyst with **Ox-0**, the ligand void of the urea moiety, led to lower conversion. The SupraBox Cu(II)-complexes showed activity, even though not always giving better results comparing with those from the use of $Cu(OTf)_2$ itself. Phenyl substitution on the oxazoline ring gave no conversion at all, independently from the spacer (entries 5 and 7). Complex of **Ox-13** (entry 8) showed good activity in terms of conversion, affording the final product in 63% yield.

Unfortunatelly no promising data were obtained with respect to enantioselection. This lack in enantioselectivity hampered us from further investigation.

Better results were achieved in the Friedel-Crafts alkylation of indole with *trans*-β-nitrostyrene.The screening results are reported in Table 1.2 here below.



Entry	Metal source	Time	Yield[a] (%)	ee[b] (%)
1	$Cu(OTf)_2$	4 days	41	rac
2	$Zn(OTf)_2$	24 h	90	8



Entry	Ligand	Temp (°C)	Solvent	Time	Yield[a] (%)	ee[b] (%)
3	**Ox-3**	15	CH_2Cl_2	17 h	63	8
4	**Ox-3**	15	Toluene/CH_2Cl_2 1:1	17 h	83	8
5	**Ox-3**	15	Toluene	17 h	42	8
6	**none**	0	Toluene/ CH_2Cl_2 1:1	3 days	30	rac
7	**Ox-0**	0	Toluene/ CH_2Cl_2 1:1	3 days	90	10
8	**Ox-2**	0	Toluene/ CH_2Cl_2 1:1	3 days	43	rac
9	**Ox-3**	0	Toluene/ CH_2Cl_2 1:1	3 days	75	10
10	**Ox-4**	0	Toluene/ CH_2Cl_2 1:1	3 days	72	10
11	**Ox-7**	0	Toluene/ CH_2Cl_2 1:1	3 days	16	rac
12	**Ox-12**	0	Toluene/ CH_2Cl_2 1:1	3 days	75	20
13	**Ox-13**	0	Toluene/ CH_2Cl_2 1:1	3 days	14	10
14	**Ox-14**	0	Toluene/ CH_2Cl_2 1:1	3 days	96	rac
15	**Ox-15**	0	Toluene/ CH_2Cl_2 1:1	3 days	82	15
16	**Ox-16**	0	Toluene/ CH_2Cl_2 1:1	3 days	33	10

[a] Isolated by flash chromatography. Eluent: EDP/AcOEt 3:1
[b] Determined by HPLC. Column Chiracel OD-H, Hex/IPA 88:12, flow 0,8 mL/min
Table 1.2

First of all we compared $Cu(OTf)_2$ with $Zn(OTf)_2$ as metal source in dichloromethane at 15°C and, as expected,[89] for this substrate zinc(II) proved to be a better catalyst than copper(II) (entries 1 and 2).

[89] S-F. Lu, D-M Du, J. Xu, *Org. Lett.* **2006**, *8*, 2115; Y-X. Jia, S-F. Zhu, Y. Yang, Q-L. Zhou, *J. Org. Chem.* **2006**, *71*, 75.

The following step was based on the choice of the best solvent. Toluene, which is reported to be the best solvent, did not work in our case due to the insolubility of our complexes in this solvent, whereas a mixture of toluene/dichloromethane in a 1:1 ratio turned out to be the best compromise.

Once the solvent was defined, we proceeded with the investigation of the ligands library, using 5 mol% of catalyst, stirring the reaction at 0°C for 3 days.

From the library of SupraBox, some representative ligands were chosen and tested.

$Zn(OTf)_2$ itself catalyzed the reaction, affording the desired product in a 30% yield (entry 6). In addition, also the complex formed from **Ox-0**, the ligand devoid of urea group, had a very good activity, leading to the final product in 90% yield (entry 7). With some complexes, higher conversions than entry 6 were obtained and in some cases (**Ox-12** and **Ox-15)** a glimmer of enantiodiscrimination was obtained (entries 12 and 15). To confirm the presence of supramolecular bidentate ligand in the reaction we compared the reaction outcome using 5 mol% $Zn(OTf)_2$ and either 5 mol% of ligand **Ox-12** (in a 1:1 ratio) or 10 mol% of the same ligand (in a 1:2 ratio). In the latter case the ee% was higher than in the first experiment, where a racemate was formed in the same yield of entry 6 (where $Zn(OTf)_2$ itself was the catalyst).

The levels of ee% reached were, unfortunately, considered not so satisfactory to lead us in continuing with further investigations.

1.8.3.2 Kinetic resolution of racemic diols and desymmetrization of meso diols

The importance of chirality is well recognized, mainly in connection with the fact that nearly all natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which interact only with molecules of the proper absolute configuration. Thus, the use of chiral drugs in enantiopure form is now a standard requirement for virtually every new chemical entity and the development of new synthetic methods to obtain enantiopure compounds has become a key goal for pharmaceutical companies. The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, as well as components in electronic and optical devices or in polymers with novel properties and lastly as probes of biological function, has made asymmetric synthesis a prominent area of investigation.

In pharmaceuticals, as well as in related industries, asymmetry plays an important role, since both enantiomers of a specific drug do not necessarily have the same activity. Although

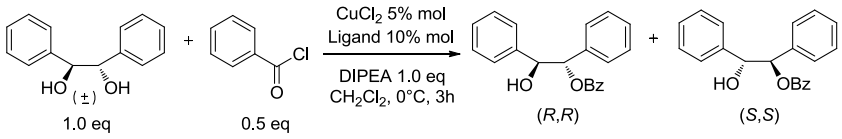
tremendous advances have been made in asymmetric synthesis, resolution of racemates is still the most important industrial approach to the synthesis of enantiomerically pure compounds.

A kinetic resolution is defined as a process where the two enantiomers of a racemate are transformed to products at different rates. If the kinetic resolution is efficient, one of the enantiomers of the racemic mixture is transformed into the desired product while the other is recovered unchanged.

Copper bis(oxazoline) complexes have been shown to be efficient catalysts in the kinetic resolution of racemic diols and in particular hydrobenzoin.

For this reason we decided to screen our small library of ligands in this reaction (Table 1.3).

The catalytic reactions were carried out by pre-formation of the complexes by stirring a suspension of $CuCl_2$ in a solution of the ligand in CH_2Cl_2, until all of the highly insoluble copper salt becomes soluble by complexation (formation of a deeply colored solution) with the ligand.



Entry	Ligand	Yield[a] (%)	ee[b] (%) (conf.)	Selectivity[c] (s) (%)
1	**Ox-0**	40	0	1
2	**Ox-1**	45	86 (*S*,*S*)	28
3	**Ox-2**	43	70 (*R*,*R*)	9.5
4	**Ox-3**	44	86 (*R*,*R*)	27
5	**Ox-4**	47	20 (*S*,*S*)	1.8
6	**Ox-5**	45	2 (*R*,*R*)	1.1
7	**Ox-6**	41	44 (*R*,*R*)	3.4
8	**Ox-7**	44	64 (*R*,*R*)	7.4
9	**Ox-8**	26	56 (*S*,*S*)	4.3
10	**Ox-9**	37	22 (*R*,*R*)	1.8
11	**Ox-10**	43	70 (*R*,*R*)	9.5
12	**Ox-11**	35	0	1
13	**Ox-12**	38	34 (*R*,*R*)	2.5
14	**Ox-13**	17	12 (*R*,*R*)	1.3

15	**Ox-14**	39	14 (*R*,*R*)	1.4
16	**Ox-15**	28	14 (*S*,*S*)	1.4
17	**Ox-16**	34	20 (*R*,*R*)	1.7

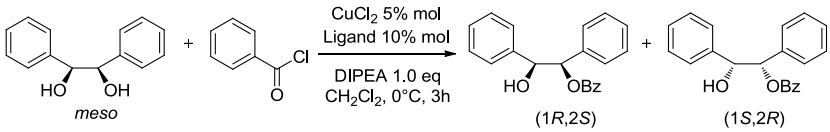
[a] Isolated by flash chromatography. Eluent: Hex/AcOEt 3:1
[b] Determined by HPLC. Column Chiralpak AS-H, Hex/IPA 90:10, flow 0,5 mL/min
[c] Determined according ref. 90
Table 1.3

Despite structural similarities between **Ox 1-16**, their performance in the asymmetric benzoylation varied considerably, and rather surprisingly, best selectivities were obtained with ligands **Ox-1** and **Ox-3**, while ligands **Ox-2** and **Ox-4**, having benzyl and phenyl substitution at the stereocenters, that had proven most successful in the title reaction with bis(oxazolines), gave inferior results.[91]

From a closer inspection of the selectivities, the importance of a fine balance of conformational flexibility, steric hindrance, and electronic properties becomes evident. In particular, the *meta*-disubstituted aromatic linker (entries 14-16) and the C_α-tetrasubstituted amino acid (Aib) hamper enantioselectivity, probably because of the high rigidity which does not allow an efficient docking of the two urea functionalities. In fact, the use of a β-alanine linker (entries 1-7), which is best combined with an *iso*-propyl or ethyl substitution at the oxazoline moiety, results in a significant increase of selectivity (entries 2 and 4). Finally, no selectivity was obtained with the monodentate ligand **Ox-0**, which is not capable of supramolecular interactions (entry 1).

The asymmetric catalytic acylation with copper(II) complexes has also been applied to the desymmetrization of *meso*-diols,[92] although with lower *ee*s than the kinetic resolution (ee = 58% in the asymmetric benzoylation of *meso*-hydrobenzoin[93]). We tested a selection of ligands in the desymmetrization of *meso*-hydrobenzoin by benzoylation and the results are collected in Table 1.4.

[90] H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249; J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5.
[91] Y. Matsumura, T. Maki, K. Tsurumaki, O. Onomura, *Tetrahedron Lett.* **2004**, *45*, 9131; C. Mazet, S. Roseblade, V. Köhler, A. Pfaltz, *Org. Lett.* **2006**, *8*, 1879; Y. Matsumura, T. Maki, S. Murakami, O. Onomura, *J. Am. Chem. Soc.* **2003**, *125*, 2052; A. Gissibl, M. G. Finn, O. Reiser, *Org. Lett.* **2005**, *7*, 2325; A. Gissibl, C. Padié, M. Hager, F. Jaroschik, R. Rasappan, E. Cuevas-Yañez, C.-O. Turrin, A.-M. Caminade, J.-P. Majoral, O. Reiser, *Org. Lett.* **2007**, *9*, 2895; A. Schätz, M. Hager, O. Reiser, *Adv. Funct. Mater.* **2009**, *19*, 2109; A. Schätz, R. N. Grass, Q. Kainz, W. J. Stark, O. Reiser, *Chem. Mater.* **2010**, *22*, 305.
[92] C. Mazet, V. Köhler, A. Pfaltz, *Angew. Chem. Int. Ed.* **2005**, *44*, 4888; D. Nakamura, K. Kakiuchi, K. Koga, R. Shirai *Org. Lett.* **2006**, *8*, 6139; Y. Demizu, K. Matsumoto, O. Onomura, Y Matsumura, *Tetrahedron Lett.* **2007**, *48*, 7605.
[93] C. Mazet, V. Köhler, A. Pfaltz, *Angew. Chem. Int. Ed.* **2005**, *44*, 4888.



Entry	Ligand	Yield[a] (%)	ee[b] (%) (conf.)
1	**Ox-0**	73	0
2	**Ox-1**	92	78 (1*S*,2*R*)
3	**Ox-2**	77	6 (1*R*,2*S*)
4	**Ox-3**	44	88 (1*R*,2*S*)
5	**Ox-4**	70	24 (1*S*,2*R*)
6	**Ox-6**	89	38 (1*R*,2*S*)
7	**Ox-7**	88	68 (1*R*,2*S*)
8	**Ox-8**	99	26 (1*S*,2*R*)
9	**Ox-9**	68	40 (1*R*,2*S*)
10	**Ox-10**	62	20 (1*R*,2*S*)
11	**Ox-13**	68	2 (1*R*,2*S*)
12	**Ox-15**	74	7 (1*S*,2*R*)

[a] Isolated by flash chromatography. Eluent: Hex/AcOEt 3:1
[b] Determined by HPLC. Column Chiralpak AS-H, Hex/IPA 90:10, flow 0,5 mL/min
Table 1.4

Once again satisfactory results were obtained with ligands **Ox-1** and **Ox-3** (entries 2 and 4). Notably, the SupraBox ligands outperform the classical methylene-bridged bis(oxazolines) and the *aza*-bis(oxazolines), probably because the flexibility of the linker allows these *meso*-substrates to be accommodated in the copper(II) coordination sphere. On the contrary, the rigidity of the classical bis(oxazolines) creates a cavity where the C_2-symmetric (*D*,*L*)-*vic*-diols can fit better than the σ-symmetric *meso*-diols. Also in this case, ligand **Ox-0**, devoid of functionalities acting as hydrogen bond donors, catalyzed the benzoylation in an unselective way (entry 1).

1.9 Conclusions

In this chapter we reported the synthesis of a new class of supramolecular bis(oxazolines), called SupraBox, using the urea moiety as self-assembly inducer.

A library of 16 ligands, with different degrees of structural diversity was prepared by a 3-step modular synthesis starting from readily available starting materials. Zinc(II)-, palladium(II)- and copper(II)-complexes were characterized by NMR spectroscopy, UV-Vis spectroscopy and Mass-spectrometry in order to investigate their structures and properties.

Zinc(II)-complexes were used as catalysts in asymmetric Friedel-Crafts alkylations of indole as well as copper(II)-complexes; whereas for kinetic resolutions of racemic diols and for the desymmetrization of *meso* diols only copper(II)-complexes were applied.

Complexes of SupraBox ligands proved to be active catalysts in the Friedel-Crafts alkylation of indole, but not entirely satisfactory results have been archived so far.

Complexes of SupraBox ligands proved to give best results in the asymmetric benzoylation of hydrobenzoin and good enantiomeric excesses were achieved with both racemic and *meso* substrates. This unusual property, and the selectivity itself, proved to be correlate to the ligand structure, and in general the more flexible ligands gave better results. We hypothesized that the above mentioned flexibility, peculiar of our system but not of classical Box and aza-Box, best fit to the structure of *meso* compounds, thus leading better results (Scheme 1.28).

In case of racemic substrates, the two enantiomers have different affinity with the catalyst, while with *meso* substrates, only one hydroxy group is available for the reactivity.

RACEMIC SUBSTRATES MESO SUBSTATES

Scheme 1.28

1.10 Experimental section

General Remarks

All reactions were carried out under a nitrogen atmosphere, using standard Schlenk techniques. The reactions were performed with distilled solvents. CH_2Cl_2 was distilled from CaH_2 and toluene was distilled from Na under nitrogen.

Kinetic resolution and desimmetrization of diols were performed using dry solvents (over molecular sieves in bottles with crown caps) purchased from Sigma–Aldrich and stored under nitrogen.

Air sensitive liquids and solutions were transferred via a gas-tight syringe or cannula.

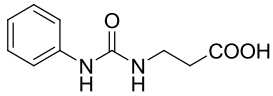
Removal of solvents was accomplished by evaporation on a Buchi rotary evaporator (water bath 40°C).

The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness). Visualisation was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution or a nynhidrine solution. Flash column chromatography was performed using silica gel (60 Å, particle size 40-64 μm) as stationary phase, following the procedure by Still and co-workers.[94] ^{1}H- and ^{13}C-NMR spectra were recorded measured on a Bruker DRX 400MHz. Chemical shifts are reported in ppm with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded with a 400 MHz spectrometer operating at 100.56 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.23 ppm). Mass spectra were measured with a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics)-4.7 T Magnet (Magnex) equipped with ESI source. Chiral HPLC analysis were performed with a Shimadzu instrument equipped with a Diode Array detector.

Commercially available reagents were used as received without, unless indicated otherwise.

1.10.1 Synthesis of the ligand relative precursors

3-(3-phenylureido)propanoic acid (**54a**)



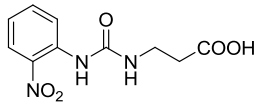
Phenylisocyanate (5.0mL, 44 mmol, 1.0 equiv.) was dissolved in 220 mL THF and then β-alanine (3.92 g, 44 mmol, 1.0 equiv.) was added and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et_2O to provide the precipitation of the product. After filtration the crude product was purified by flash chromatography eluting

[94] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

with 3→10% MeOH in DCM to yield product **54a** as fine white powder (8.33g, 40 mmol, 91%).

R*f* = 0.24 (DCM/MeOH 95:5) - m.p.160-161°C - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 2.55 (t, 2H, *J*= 6.3 Hz), 3.47 (t, 2H, *J*= 6.3 Hz), 6.98 (t, 1H, *J*= 6.8 Hz), 7.25 (dd, 2H, *J*= 8.4, 7.4 Hz), 7.33 (m, 2H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ = 34.1, 35.2, 119.0, 122.0, 128.4, 139.5, 156.8, 174.3. - **IR:** ν = 3584, 3329, 2725, 1694, 1638, 1571, 1108. - $C_{10}H_{12}N_2O_3$ (208.21): calcd. C 57.68, H 5.81, N 13.45; found C 57.73, H 5.57, N 13.81.

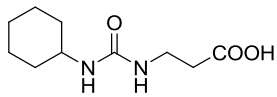
3-(3-(2-nitrophenyl)ureido)propanoic acid (**54b**)



2-nitro-phenylisocyanate (1.000 g, 6.09 mmol, 1.0 equiv.) was dissolved in 30 mL THF and then β-alanine (1.085 g, 12.18 mmol, 2.0 equiv.) was added and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et_2O to provide the precipitation of the product. After filtration the crude product was purified by flash chromatography eluting with 3→5% MeOH in DCM to yield product **54b** as fine yellow powder (1.077g, 4.25 mmol, 67%).

R*f*= 0.41 (DCM/MeOH 95:5) - m.p.160-161°C - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 2.56 (t, 2H, *J*= 6.6 Hz), 3.48 (t, 2H, *J*= 6.6 Hz), 7.13 (ddd, 1H, *J*= 8.5, 7.2, 1.3), 7.61 (ddd, 1H, *J*= 8.6, 7.2, 1.6), 8.12 (dd, 1H, *J*= 8.5, 1.6 Hz), 8.35 (dd, 1H, *J*= 8.6, 1.3 Hz). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ = 33.8, 35.5, 121.4, 122.1, 125.1, 134.6, 135.7, 137.1, 155.4, 174.0. - **IR:** ν = 3583, 3393, 3330, 2753, 2360, 1694, 1611, 1582, 1539, 1342, 1258, 1142, 1085, 798. - $C_{10}H_{11}N_3O_5$ (253.21): calcd. C 47.43; H 4.38; N 16.59; found C 47.62, 4.23, 16.2

3-(3-cyclohexylureido)propanoic acid (**54c**)

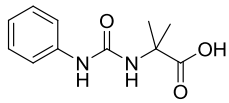


Cyclohexylisocyanate (2.86 mL, 22 mmol, 1.0 equiv.) was dissolved in 150 mL THF and then β-alanine (2.00 g, 22.4 mmol, 1.0 equiv.) was added and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et_2O to provide the precipitation of the product. After filtration the crude product was purified by flash

chromatography eluting with 5→15% MeOH in DCM to yield product **54c** as fine white powder (3.60 g, 16.8 mmol, 76%).

R*f*= 0.23 (DCM/MeOH 95:5) - m.p.159-160°C - **^{1}H NMR** (400 MHz, DMSO, 25°C): δ = 0.97-1.16 (m, 3H), 1.18-1.30 (m, 2H), 1.50 (m, 1H), 1.61 (m, 1H), 1.70 (m, 1H), 2.31 (t, 2H, *J*= 6.5 Hz), 3.15 (q, 2H, *J*= 6.5 Hz), 5.74 (t, 1H, *J*= 5.8 Hz), 5.83 (d, 1H, 7.9 Hz), 12.17 (s,1H). - **^{13}C NMR** (100.6 MHz, DMSO, 25°C): δ = 24.9, 25.8, 33.7, 35.5, 35.7, 48.1, 157.7, 173.9. - **IR:** ν = 3335, 1699, 1626, 1580, 1535, 1307, 1248, 1222, 1080, 921. - $C_{10}H_{18}N_2O_3$ (214.26): calcd. C 56.06; H 8.47; N 13.07; found C 55.87, H 8.62, N 12.72.

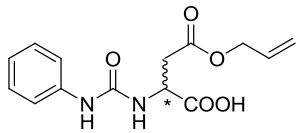
2-methyl-2-(3-phenylureido)propanoic acid (**54d**)



2-aminoisobutyric acid (3.0 g, 29 mmol, 1.3 equiv) was suspended in 10 mL of 2M NaOH then phenylisocyanate (2.37 mL, 22 mmol, 1.0equiv) was added and the mixture reaction was stirred for 60 minutes at room temperature. The mixture was filtered and the product was precipitated from solution by slow addition of 1M HCl. The white solid was dissolved in 10 mL of 1M NaOH and the solution washed with DCM. Addition of 1M HCl provides the precipitation of product **54d** as fine white powder (1.73 g, 7.78 mmol, 35%).

R*f*= 0.37 (DCM/MeOH 95:5) - m.p.157-158°C - **^{1}H NMR** (400 MHz, CD_3OH, 25°C): δ = 1.53 (s, 6H), 6.41 (s, 1H), 6.95 (m, 1H), 7.24 (m, 2H), 7.30 (m, 2H), 8.19 (s, 1H). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ = 24.6, 55.3, 118.6, 121.9, 128.3, 139.4, 155.7, 177.3. - **IR:** ν= 3381, 2724, 1704, 1648, 1544, 1308, 1158, 1069. - $C_{11}H_{14}N_2O_3$ (222.24): calcd. C 59.45; H 6.35; N 12.60; found C 59.55, H 5.55, N 12.61.

4-(allyloxy)-4-oxo-2-(3-phenylureido)butanoic acid (**56a-56b**)

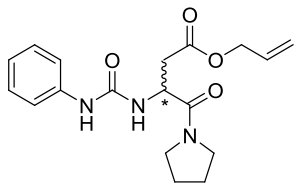


4-(allyloxy)-2-amino-4-oxobutanoic acid hydrochloride (1.20 g, 5.72 mmol, 1.0 equiv.) was suspended in 57 mLTHF and triethylamine (0.79 mL, 5.72 mmol, 1.0 equiv) added dropwise. The reaction mixture was vigorously stirred for 30 minutes then phenylisocyanate (0.65 mL, 5.72 mmol, 1.0 equiv) added and stirred for 3 days at room temperature. The mixture was treated with acold Et_2O to provide the precipitation of a white powder. The solid was washed

with $KHSO_4$ 1M to obtain product **56a** and **56b** as fine white powder (*S*-enantiomer: 1.407 g, 4.81 mmol, 84%, *R*-enantiomer: 1.394 g, 4.77 mmol, 83%.).

R*f*= 0.28 (DCM/MeOH 95:5) - m.p.186-187°C - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 2.86 (bs, 2H), 4.54 (bs, 2H), 4.78 (bs, 1H), 5.19 (d, 1H, *J*= 10.4 Hz), 5.26 (d, 1H, *J*= 17.1 Hz), 5.84 (m, 1H), 6.8 (bs, 1H), 6.96 (t, 1H, *J*= 6.8 Hz), 7.20 (t, 2H, *J*= 7.1 Hz), 7.39 (d, 2H, *J*= 7.0 Hz), 8.46 (bs, 1H), 11.23 (bs, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ = 36.5, 49.9, 65.6, 118.4, 119.4, 122.6, 128.8, 131.8, 139.1, 156.5, 170.9. - **IR:** ν = 3311, 2738, 2603, 2531, 2496, 1716, 1702, 1596, 1547, 1397, 1172, 1072, 1036, 851, 807. - $C_{14}H_{16}N_2O_5$ (292.29): calcd. C 57.53; H 5.52; N 9.58; found C 57.89, H 5.87, N 9.34.

allyl 4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanoate (**57a**-**57b**)

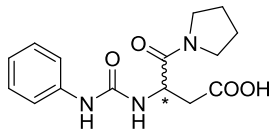


4-(allyloxy)-4-oxo-2-(3-phenylureido)butanoic acid (1.300 g, 4.45 mmol, 1.0 equiv) and N,N-diisopropylethylamine (1.90 mL, 11.1 mmol, 2.5 equiv.) were dissolved in 45 mL DMF and the solution cooled at 0°C. HBTU (1.3equiv) was added and the solution stirred at the same temperature for 30 minutes, then pirrolidine (0.44 mL, 5.34 mmol, 1.2 equiv.) was added and the reaction mixture stirred at 0°C for 60 minutes and overnight at room temperature.

The solvent was evaporated under reduced pressure and the mixture separated by flash chromatography eluting with MeOH (gradient from 2 to 6%) in DCM to yield the products **4a** and **4b** as pale yellow oil (*S*-enantiomer: 1.199 g, 3.47 mmol, 78%, *R*-enantiomer: 1.122 g, 3.24 mmol, 73%.).

R*f*= 0.28 (DCM/MeOH 95:5) - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 1.88 (m, 2H), 1.99 (m, 2H), 2.68 (dd, 1H, *J*= 15.8, 6.7 Hz), 2.89 (dd, 1H, *J*= 15.8, 7.4 Hz), 3.42 (m, 2H), 3.67 (m, 1H), 3.78 (m, 1H), 4.59 (t, 1H, *J*= 1.3 Hz), 4.61 (t, 1H, *J*= 1.3 Hz), 5.01 (t, 1H, *J*= 7.0 Hz), 5.20 (ddd, 1H, *J*= 10.5, 2.7, 1.2 Hz), 5.31 (ddd, 1H, *J*= 17.2, 3.0, 1.6 Hz), 5.92 (m, 1H), 6.98 (m, 1H), 7.24 (m, 2H), 7.34 (dd, 2H, *J*= 8.8, 1.0 Hz). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ = 23.7, 25.5, 36.6, 46.0, 46.5, 48.2, 65.1, 117.2, 118.8, 122.3, 128.4, 132.1, 139.2, 155.7, 170.2, 170.4. - **IR:** ν = 2721, 2656, 2512, 2345, 1721, 1678, 1600, 1329, 1178, 1109, 1074, 997, 856. - $C_{18}H_{23}N_3O_4$ (345.39): calcd. C 62.59; H 6.71; N 12.17; found C 62.33, H 6.57, N 11.99.

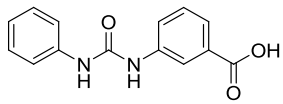
4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanoic acid (**54e**-**54f**)



allyl 4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanoate (1.10g, 3.18mmol, 1.0 equiv) was dissolved in 30mL DCM and the solution cooled at 0°C. Pyrrolidine (0.31 mL, 3.82 mmol, 1.2 equiv.), triphenylphosphane (0.149 g, 0.57 mmol, 0.18 equiv.) and tetrakis(triphenylphosphane) palladium(0) (0.147 g, 0.13 mmol, 0.04 equiv.) were added and the reaction mixture stirred for 1 hour at 0°C. The mixture was poured into AcOEt (200mL) and extracted with satd. $NHCO_3$ solution (5x 30mL). Organic layers were acidified to pH 2 with 1M $KHSO_4$ solution. The acidified aqueous solutions was extracted with DCM (3x 25mL) and the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 6% MeOH in DCM to yield the product as yellow solid (S-enantiomer 0.778 g, 2.55 mmol, 80%, *R*-enantiomer 0.754 g, 2.47 mmol, 77%.).

R*f*= 0.30 (DCM/MeOH 95:5) - m.p.168-169°C - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 1.85 (m, 2H), 1.96 (m, 2H), 2.73 (dd, 1H, *J*= 15.7, 6.2 Hz), 2.84, (dd, 1H, *J*= 15.7, 6.1 Hz), 3.44 (m, 2H), 3.62 (m, 1H), 3.80 (m, 1H), 5.13 (m, 1H), 6.75 (d, 1H, *J*= 8.8 Hz), 6.97 (t, 1H, *J*= 7.5 Hz), 7.21 (t, 2H, *J*= 7.5 Hz), 7.34 (d, 2H, *J*= 7.7 Hz), 8.08 (s, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ = 24.1, 25.9, 37.5, 46.6, 47.1, 48.2, 119.5, 122.7, 128.8, 139.1, 155.4, 170.6, 173.7. - **IR:** ν = 3347, 3202, 3145, 1728, 1685, 1615, 1553, 1518, 1481, 1312, 1203, 1119, 1046, 997. - $C_{15}H_{19}N_3O_4$ (305.33): calcd. C 59.01; H 6.27; N 13.76; found C 59.34, H 5.99, N 13.44.

3-(3-phenylureido)benzoic acid (**54g**)

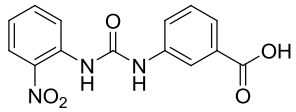


Phenylisocyanate (1.59 mL, 14.5 mmol, 1.0 equiv.) and 3-aminobenzoic acid (2.0 g, 14.5 mmol, 1.0 equiv) were dissolved in 80 mL THF and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et_2O to provide the precipitation of the product as fine white powder (2.34 g, 9.15 mmol, 63%).

R*f*= 0.35 (DCM/MeOH 95:5) - m.p.152-1531°C - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 7.03 (m, 1H), 7.30 (m, 2H), 7.37-7.46 (m, 3H), 7.68 (ddd, 1H, *J*= 7.7, 1.5, 1.1 Hz), 7.73 (ddd,

1H, *J*= 8.0, 2.3, 1.1 Hz), 8.08 (t, 1H, *J*= 1.7 Hz). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ = 119.1, 119.9, 122.6, 123.2, 123.5, 128.4, 128.6, 131.2, 139.0, 139.5, 151.1, 168.2. - **IR:** ν = 3354, 2724, 1738, 1680, 1649, 1556, 1310, 1156, 1066. - $C_{14}H_{12}N_2O_3$ (256.26): calcd. C 65.62; H 4.72; N 10.93; found C 63.38, 4.44, 10.81.

3-(3-(2-nitrophenyl)ureido)benzoic acid (**54h**)



2-nitrophenyl isocyanate (1.0 g, 6.09 mmol, 1.0 equiv.) and 3-aminobenzoic acid (0.84 g, 6.09 mmol, 1.0 equiv) were dissolved in 60 mL THF and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et_2O to provide the precipitation of the product as fine yellow powder (1.36 g, 4.50 mmol, 74%).

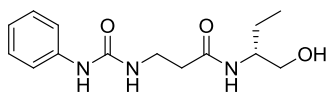
R*f*= 0.26 (DCM/MeOH 95:5) - m.p.174-175°C - **^{1}H NMR** (400 MHz, DMSO, 25°C): δ = 7.22 (ddd, 1H, *J*= 8.4, 7.2, 1.2 Hz), 7.42 (t, 1H, *J*= 7.8 Hz), 7.59 (dt, 1H, *J*=7.7, 1.2 Hz), 7.66-7.73 (m, 2H), 8.09 (dd, 1H, *J*= 8.4, 1.6 Hz), 8.15 (t, 1H, *J*= 1.8 Hz), 8.29 (dd, 1H, *J*= 8.5, 1.2 Hz), 9.61 (s, 1H), 10.03 (s, 1H), 12.93 (s, 1H). - **^{13}C NMR** (100.6 MHz, DMSO, 25°C): δ = 119.7, 122.8, 123.0, 123.7, 125.8, 129.6, 131.9, 135.2, 135.4, 138.3, 140.0, 152.3, 167.6. - **IR:** ν = 3354, 3281, 2724, 1829, 1739, 1652, 1543, 1310, 1155, 1073, 949. - $C_{14}H_{11}N_3O_5$ (301.25): calcd. C 55.82; H 3.68; N 13.95; found C 55.54, H 3.34, N 14.30.

1.10.2 General procedure for the synthesis of compounds 58

Carboxylic acid (1.1 equiv) and *N*,*N*-Diisopropylethylamine (3.0 equiv) were dissolved in DCM (0.1M solution) and the solution cooled at 0°C. HBTU (1.3 equiv) was added and the solution stirred at the same temperature for 30 minutes, then the aminoalcohol (1.0 equiv) was added and the reaction mixture stirred at 0°C for 60 minutes and overnight at room temperature.

The solvent was evaporated under reduced pressure and the mixture separated by flash chromatography eluting with MeOH (gradient from 2 to 10%) in DCM to yield the product.

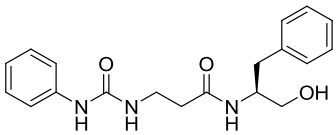
(R)-*N*-(1-hydroxybutan-2-yl)-3-(3-phenylureido)propanamide (**58a**)



According to the general procedure product **58a** was yielded as white solid (0.604 g, 2.16 mmol, 99%) starting from acid **54a** (0.500g, 2.4mmol) and coupled with (R)-2-aminobutan-1-ol.

R*f*= 0.23 (DCM/MeOH 94:6) - m.p. 131-132°C - $[\alpha]^{20}_{D}$ = +32.01(c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 0.93 (t, 3H, *J*= 7.4 Hz), 1.42 (m, 1H), 1.63 (m, 1H), 2.46 (m, 2H), 3.43-3.52 (m, 4H), 3.80 (m, 1H), 6.97 (m, 1H), 7.23 (m, 2H), 7.33 (m, 2H). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ = 18.6, 23.9, 36.5, 37.3, 53.9, 64.8, 119.8, 123.0, 128.9, 138.9, 157.0, 173.3. - **IR:** ν = 3327, 3265, 2724, 1738, 1647, 1557, 1307, 1154, 1070. - $C_{14}H_{21}N_3O_3$ (279.33): calcd. C 60.20; H 7.58; N 15.04; found C 60.42, H 7.59, N 14.79.

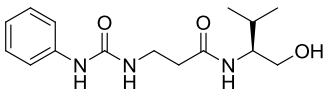
(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-3-(3-phenylureido)propanamide (**58b**)



According to the general procedure product **58b** was yielded as white solid (0.802 g, 2.35 mmol, 98%) starting from acid **54a** (0.500 g, 2.4 mmol) and coupled with (*S*)-2-amino-3-phenylpropan-1-ol.

R*f*= 0.30 (DCM/MeOH 95:5). - m.p. 131-132°C - $[\alpha]^{20}_{D}$ = -34.68 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 2.38 (t, 2H, *J*= 6.4 Hz), 2.71 (dd, 1H, *J*= 13.8, 8.1), 2.90 (dd, 1H, *J*= 13.8, 6.2 Hz), 3.38 (m, 2H), 3.53 (m, 2H), 4.12 (m, 1H), 6.97 (m, 1H), 7.15 (m, 1H), 7.21-7.27 (m, 6H), 7.33 (m, 2H). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 35.9, 36.1, 36.6, 52.8, 62.9, 118.8, 122.1, 125.9, 126.9, 127.9, 128.4, 128.9, 138.4, 139.5, 156.8, 172.5. - **IR:** ν = 3320, 2724, 2453, 1829, 1738, 1625, 1545, 1308, 1263, 1156, 1071, 1036. - $C_{19}H_{23}N_3O_3$ (341.40): calcd. C 66.84; H 6.79; N 12.31; found C 67.01, H 6.46, N 12.37.

(*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-3-(3-phenylureido)propanamide (**58c**)

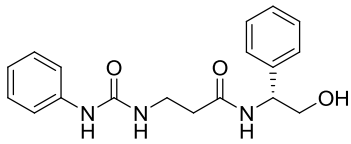


According to the general procedure product **58c** was yielded as white solid solid (0.569 g, 1.94 mmol, 89%) starting from the acid **54a** (0.500 g, 2.4 mmol) and coupled with *L*-valinol.

R*f*= 0.22 (DCM/MeOH 95:5). - m.p. 121-122°C - $[\alpha]^{20}_{D}$ = -31.01(c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 0.89 (d, 3H, *J*= 6.8 Hz), 0.91 (d, 3H, *J*= 6.8 Hz), 1.83 (m, 1H), 2.57 (m, 2H), 2.90 (bs, 1H), 3.47-3.59 (m, 3H), 3.67 (dd, 1H, *J*= 11.6, 3.2 Hz), 3.75 (m, 1H),

6.85 (d, 1H, *J*= 8.5 Hz), 6.98 (m, 1H), 7.21 (m, 2H), 7.28 (m, 1H), 7.44 (m, 1H), 7.55 (m, 1H), 7.86 (bs, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ = 18.9, 19.4, 29.1, 36.5, 37.2, 57.4, 63.3, 119.8, 123.1, 128.9, 138.7, 156.9, 173.4. - **IR:** ν = 3337, 3243, 3087,2478, 2419, 1670, 1632, 1560, 1503, 1354, 1295, 1260, 1141, 1117, 1063, 1029, 970, 760. - $C_{15}H_{23}N_3O_3$ (293.36): calcd. C 61.41; H 7.90; N 14.32; found C 61.21, H 8.02, N 14.72.

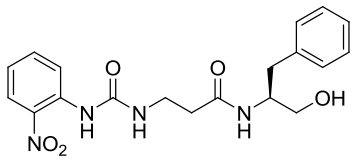
(*R*)-*N*-(2-hydroxy-1-phenylethyl)-3-(3-phenylureido)propanamide (**58d**)



According to the general procedure product **58d** was yielded as white solid (0.505 g, 1.54 mmol, 64%) starting from acid **54a** (0.500 g, 2.4 mmol) and coupled with (*R*)-2-amino-2-phenylethanol.

R*f*= 0.31 (DCM/MeOH 95:5). - m.p. 119-120°C - $[\alpha]^{20}_D$ = -37.23 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 2.53 (m, 2H), 3.47 (t, 2H, *J*= 6.5 Hz), 3.77 (dd, 1H, *J*= 11.2, 7.7 Hz), 3.75 (dd, 1H, *J*= 11.2, 5.3 Hz), 5.01 (dd, 1H, *J*= 7.7, 5.3 Hz), 6.97 (tt, 1H, J= 7.3, 1.2 Hz), 7.20-7.35 (m, 9H). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 35.9, 36.0 55.6, 64.9, 118.8, 122.0, 126.6, 127.0, 128.1, 128.4, 139.5, 139.9, 156.8, 172.5. - **IR:** ν = 3382, 3308, 2462, 2364, 1644, 1598, 1544, 1313, 1243, 1153, 1125, 1078, 1056, 905. - $C_{18}H_{21}N_3O_3$ (327.38): calcd. C 66.04; H 6.47; N 12.84; found C 65.89, H 6.75, N 12.56.

(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-3-(3(2nitrophenyl)ureido) propanamide (**58e**)

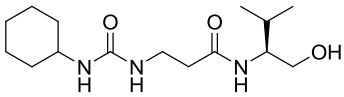


According to the general procedure product **58e** was yielded as yellow solid (0.211 g, 0.546 mmol, 46%) starting from acid **54b** (0.300 g, 1.18 mmol) and coupled with (*S*)-2-amino-3-phenylpropan-1-ol.

R*f* = 0.31 (DCM/MeOH 95:5). - m.p. 146-147°C - $[\alpha]^{20}_D$ = -43.40 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 2.40 (t, 2H, *J*= 6.6 Hz), 2.72 (dd, 1H, *J*= 13.7, 8.3), 2.90 (dd, 1H, *J*= 13.7, 6.1 Hz), 3.41 (m, 2H), 3.51 (dd, 1H, *J*= 11.1, 5.6 Hz), 3.56 (dd, 1H, *J*= 10.6, 5.1 Hz), 4.14 (m, 1H), 7.13 (m, 2H), 7.23 (m, 4H), 7.61 (ddd, 1H, *J*= 8.7, 7.2, 1.6), 8.13 (dd, 1H,

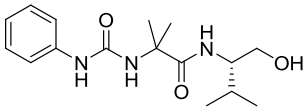
J= 8.4, 1.6 Hz), 8.35 (dd, 1H, *J*= 8.6, 1.2 Hz). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 35.9, 36.2, 36.6, 52.8, 62.8, 121.4, 122.1, 125.1, 125.9, 127.8, 128.9, 134.6, 135.7, 137.1, 138.4, 155.4, 172.2. - **IR:** ν = 3371, 3329, 3282, 2368, 1676, 1649, 1585, 1556, 1155, 1116, 1082, 960, 840. - $C_{19}H_{22}N_4O_5$ (355.43): calcd. C 59.06; H 5.74; N 14.50; found C 59.23, H 6.00, 14.76.

(*S*)-3-(3-cyclohexylureido)-*N*-(1-hydroxy-3-methylbutan-2-yl)propanamide (**58f**)



According to the general procedure product **58f** was yielded as white solid (0.688 g, 2.19 mmol, 99%) starting from acid **54c** (0.500 g, 2.3 mmol) and coupled with *L*-Valinol.
R*f* = 0.44 (DCM/MeOH 95:5). - m.p. 140-141°C - $[\alpha]^{20}_D$ = -30. 12 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 0.91 (d, 3H, *J*= 6.7 Hz), 0.94 (d, 3H, *J*= 6.7 Hz), 1.17 (m, 3H), 1.34 (m, 3H), 1.60 (dt, 1H, *J*= 12.6, 3.8 Hz), 1.72 (dt, 1H, *J*= 13.3, 3.8 Hz), 1.85 (m, 3H), 2.42 (m, 2H), 3.39 (m, 2H), 3.53 (dd, 1H, *J*= 11.4, 6.6 Hz), 3.61 (dd, 1H, *J*= 11.3, 4.4 Hz), 3.71 (m, 1H). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 17.4, 18.6, 24.6, 25.3, 28.6, 33.3, 36.1, 36.5, 56.6, 61.9, 158.9, 172.9. - **IR:** ν = 3312, 3278, 2409, 1623, 1578, 1545, 1345, 1214, 1123,1076, 965. - $C_{15}H_{29}N_3O_3$ (299.41): calcd. C 60.17; H 9.76; N 14.03; found C 59.89, H 10.09, 14.33.

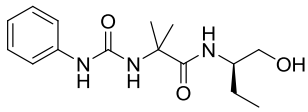
(*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-(3-phenylureido) propanamide (**58g**)



According to the general procedure product **58g** was yielded as white solid (0.630 g, 2.04 mmol, 100%) starting from acid **54d** (0.500 g, 2.25 mmol) and coupled with *L*-Valinol.
R*f* = 0.25 (DCM/MeOH 95:5) - m.p. 135-136°C - $[\alpha]^{20}_D$ = -38.27 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 0.86 (d, 3H, *J*= 6.8 Hz), 0.89 (d, 3H, *J*= 6.7 Hz), 1.52 (s, 3H), 1.53 (s, 3H), 1.70 (m, 1H), 3.39 (t, 1H, *J*= 10.2 Hz), 3.70 (m, 2H), 3.98 (bs, 1H), 6.43 (s, 1H), 6.86 (d, 1H, *J*= 9.8 Hz), 6.94 (t, 1H, *J*= 7.2 Hz), 7.15 (t, 2H, 7.6 Hz), 7.28 (d, 2H, 7.7 Hz), 8.09 (s, 1H). - **^{13}C NMR** (100.6 MHz, $CHCl_3$, 25°C): δ= 19.2, 19.7, 24.7, 26,9 29.1, 56.8, 57.9, 64.2, 120.1, 123.0, 128.7, 138.7, 156.1, 177.4. - **IR:** ν = 3358, 2724, 1649, 1578, 1542,

1310, 1150, 1133, 1087, 965. - $C_{16}H_{25}N_3O_3$ (307.39): calcd. C 62.52; H 8.20; N 13.67; found C 62.22, H 8.06, N 14.01.

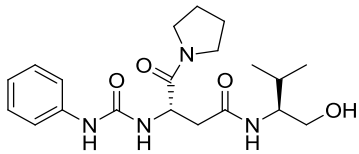
(*R*)-*N*-(1-hydroxybutan-2-yl)-2-methyl-2-(3-phenylureido)propanamide (**58h**)



According to the general procedure product **58h** was yielded as white solid (0.630 g, 2.04 mmol, 100%) starting from acid **54d** (0.500 g, 2.25 mmol) and coupled with (*R*)-2-aminobutan-1-ol.

R*f* = 0.27 (DCM/MeOH 95:5). - m.p. 137-138°C - $[\alpha]^{20}_D$ = +39.99 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 0.94 (t, 3H, *J*= 7.6 Hz), 1.46 (m, 1H), 1.50 (s, 6H), 1.62 (m, 1H), 3.52 (d, 2H, *J*= 5.4 Hz), 3.81 (m, 1H), 6.97 (t, 1H, *J*= 7.3 Hz), 7.23 (m, 2H), 7.33 (dd, 2H, *J*= 8.5, 1.0 Hz). - **^{13}C NMR** (100.6 MHz, $CHCl_3$, 25°C): δ= 10.6, 23.4, 24.8, 26.9, 53.9, 56.7, 65.6, 120.0, 123.0, 128.7, 138.7, 156.0, 177.4. - **IR:** ν = 3382, 3271, 3133, 2724, 1648, 1598,1542, 1494, 1312, 1253, 1220, 1168, 1062, 845. - $C_{15}H_{23}N_3O_3$ (293.36): calcd. C 61.41; H 7.90; N 14.32; found C 61.22, H 8.01, N 13.97.

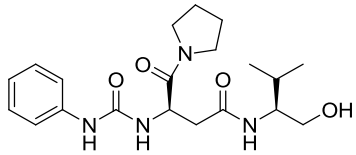
(*S*)-*N*-((*S*)-1-hydroxy-3-methylbutan-2-yl)-4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanamide (**58i**)



According to the general procedure product **58i** was yielded as yellow pale oil (0.154 g, 0.39 mmol, 60%) starting from the acid **54e** (0.200 g, 0.65 mmol) and coupled with *L*-valinol.

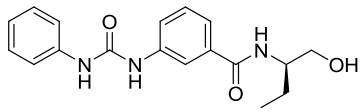
R*f* = 0.33 (DCM/MeOH 95:5).- $[\alpha]^{20}_D$ = -78.04 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 0.91 (d, 3H, *J*= 6.8 Hz), 0.94 (d, 3H, 6.7 Hz), 1.82-1.93 (m, 2H), 2.00 (m, 1H), 2.57 (dd, 1H, *J*= 14.4, 7.4 Hz), 2.72 (dd, 1H, *J*= 14.4, 6.7 Hz), 3.38-3.60 (m, 4H), 3.69 (m, 2H), 3.79 (m, 1H), 5.02 (t, 1H, *J*= 7.2 Hz), 6.98 (m, 1H), 7.24 (m, 2H), 7.33 (m, 2H). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 17.4, 18.6, 23.7, 25.5, 28.5, 38.4, 45.9, 46.5, 48.8, 56.7, 61.7, 118.8, 122.2, 128.4, 139.2, 155.8, 170.7. - **IR:** ν = 3310, 3259, 2767, 2456, 2412, 1665, 1565, 1508, 1459, 1334, 1300, 1211, 1098, 980, 876. - $C_{20}H_{30}N_4O_4$ (390.48): calcd. C 61.52; H 7.74; N 14.35; found C 61.66, H 7.60, N 14.53.

(*R*)-*N*-((*S*)-1-hydroxy-3-methylbutan-2-yl)-4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanamide (**58j**)



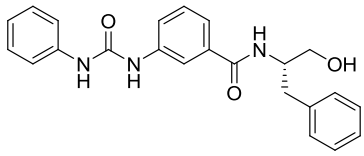
According to the general procedure product **58j** was yielded as yellow pale oil (0.144 g, 0.37 mmol, 56%) starting from the acid **54f** (0.200 g, 0.65 mmol) and coupled with *L*-valinol.
R*f* = 0.33 (DCM/MeOH 95:5). - $[\alpha]^{20}_{D}$ = -12.35 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 0.89 (d, 3H, *J*= 6.8 Hz), 0.93 (d, 3H, *J*= 6.7 Hz), 1.80-1.92 (m, 3H), 2.00 (m, 2H), 2.58 (dd, 1H, *J*= 14.3, 6.8 Hz), 2.73 (dd, 1H, *J*= 14.3, 7.4 Hz), 3.35-3.63 (m, 4H), 3.70 (m, 2H), 3.82 (m, 1H), 4.99 (t, 1H, *J*= 7.0 Hz), 6.98 (m, 1H), 7.24 (m, 2H), 7.33 (dd, 2H, *J*= 8.8, 1.2 Hz). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 17.3, 18.6, 23.7, 25.5, 28.5, 38.3, 45.9, 46.5, 48.7, 56.7, 61.7, 118.7, 122.2, 128.4, 139.2, 155.8, 170.6, 170.8. - **IR:** ν = 3300, 3256, 2789, 2481, 2426, 1656, 1599, 1548, 1499, 1315, 1224, 1100, 978, 856. - $C_{20}H_{30}N_4O_4$ (390.48): calcd. C 61.52; H 7.74; N 14.35; found C 61.84, H 7.70, N 14.39.

(*R*)-*N*-(1-hydroxybutan-2-yl)-3-(3-phenylureido)benzamide (**58k**)



According to the general procedure product **58k** was yielded as white solid (0.565 g, 1.72 mmol, 97%) starting from acid **54g** (0.500 g, 1.95 mmol) and coupled with (*R*)-2-aminobutan-1-ol.
R*f* = 0.40 (DCM/MeOH 95:5). - m.p. 146-147°C - $[\alpha]^{20}_{D}$ = +42.58 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 1.00 (t, 3H, *J*= 7.5 Hz), 1.56 (m, 1H), 1.76 (m, 1H), 3.63 (dd, 2H, *J*= 5.6, 0.9 Hz), 4.03 (m, 2H), 7.03 (t, 1H, *J*= 7.3 Hz), 7.29 (dd, 2H, *J*= 8.5, 7.5 Hz), 7.36 (t, 1H, *J*= 7.8 Hz), 7.44 (dd, 2H, *J*= 8.7, 1.2 Hz), 7.48 (dt, 1H, *J*= 7.7, 1.3 Hz), 7.58 (ddd, 1H, *J*= 7.9, 2.2, 1.1 Hz), 7.88 (t, 1H, *J*= 1.8 Hz), 8.05 (d, 1H, *J*= 8.3 Hz). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 9.6, 23.66, 53.7, 63.43, 117.9, 119.1, 121.2, 121.9, 122.6, 128.5, 128.7, 135.6, 138.9, 139.4, 153.9, 169.2. - **IR:** ν = 3383, 2724, 1697, 1648, 1542, 1154, 1069. - $C_{18}H_{21}N_3O_3$ (327.38): calcd. C 66.04; H 6.47; N 12.84; found C 65.93, H 6.70, N 12.58.

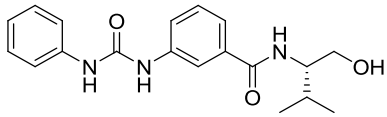
(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-3-(3-phenylureido)benzamide (**58l**)



According to the general procedure product **58l** was yielded as white solid (0.689 g, 1.77 mmol, 100%) starting from acid **54g** (0.500 g, 1.95 mmol) and coupled with (S)-2-amino-3-phenylpropan-1-ol.

R*f* = 0.34 (DCM/MeOH 95:5). - m.p. 157-158°C - $[\alpha]^{20}_{D}$ = -50.29 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 2.87 (dd, 1H, *J*= 13.7, 8.6 Hz), 3.03 (dd, 1H, J= 13.7, 6.2 Hz), 3.66 (d, 2H, *J*= 5.5 Hz), 4.34 (m, 1H), 7.04 (t, 1H, *J*= 7.5 Hz), 7.17 (m, 1H), 7.29 (m, 6H), 7.37 (m, 2H), 7.45 (dd, 2H, *J*= 8.6, 1.0 Hz), 7.56 (dt, 1H, *J*= 7.0, 2.2 Hz), 7.79 (m, 1H). – **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 36.6, 53.6, 62.9, 117.8, 119.0, 121.1, 121.8, 122.6, 125.9, 128.0, 128.5, 128.6, 129.0, 134.7, 135.5, 138.5, 139.0, 139.3, 153.9, 168.8. - **IR:** ν = 3324, 2724, 1739, 1648, 1543, 1310, 1265, 1155, 1069, 876, 840. - $C_{23}H_{23}N_3O_3$ (389.45): calcd. C 70.93; H 5.95; N 10.79; found C 70.88, H 6.18, N 7.78.

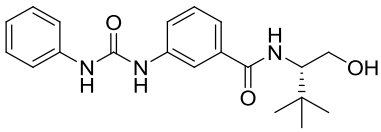
(*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-3-(3-phenylureido)benzamide (**58m**)



According to the general procedure product **58m** was yielded as white solid (0.578 g, 1.69 mmol, 96%) starting from acid **54g** (0.500 g, 1.95 mmol) and coupled with *L*-Valinol

R*f* = 0.38 (DCM/MeOH 95:5). - m.p. 167-168°C - $[\alpha]^{20}_{D}$ = -44.37 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 1.00 (d, 3H, *J*= 6.8 Hz), 1.03 (d, 3H, *J*= 6.8 Hz), 2.00 (m, 1H), 3.67-3.76 (m, 2H), 3.91 (m, 1H), 7.03 (t, 1H, *J*= 7.3 Hz), 7.30 (m, 2H), 7.39 (t, 1H, *J*= 7.9 Hz), 7.44 (dd, 2H, *J*= 8.7, 1.2 Hz), 7.48 (dt, 1H, *J*= 7.7, 1.3 Hz), 7.58 (ddd, 1H, *J*= 8.1, 2.1, 1.0 Hz), 7.88 (t, 1H, *J*= 1.8 Hz). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 17.8, 18.7, 28.9, 57.4, 61.7, 117.9, 119.0, 121.2, 121.8, 122.6, 128.4, 128.6, 135.7, 138.9, 139.4, 153.9, 169.2. - **IR:** ν = 3266, 3200, 2722, 1656, 1609, 1565, 1501, 1310, 1221, 1167, 1089, 989, 840. - $C_{19}H_{23}N_3O_3$ (341.40): calcd. C 66.84; H 6.79; N 12.31; found C 66.62, H 7.14, N 12.14.

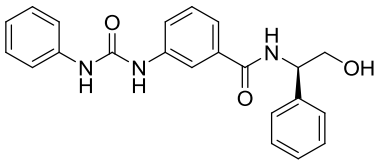
(*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-3-(3-phenylureido)benzamide (**58n**)



According to the general procedure product **58n** was yielded as white solid (0.552 g, 1.55 mmol, 88%) starting from acid **54g** (0.500 g, 1.95 mmol) and coupled with (*S*)-2-amino-3,3-dimethylbutan-1-ol.

R*f* = 0.37 (DCM/MeOH 95:5). - m.p. 97-98°C - $[\alpha]^{20}_{D}$ = -49.69 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 1.02 (s, 9H), 3.63 (dd, 1H, *J*= 11.4, 8.8 Hz), 3.68 (dd, 1H, *J*= 11.4, 3.5 Hz), 4.04 (dd, 1H, *J*= 8.8, 3.5 Hz), 7.04 (m, 1H), 7.30 (m, 1H), 7.40 (t, 1H, *J*= 7.7 Hz), 7.42-7.50 (m, 3H), 7.59 (ddd, 1H, *J*= 7.9, 2.2, 1.1 Hz) 7.87 (t, 1H, *J*= 1.7 Hz) - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 26.0, 33.9, 54.4, 60.9, 117.9, 119.1, 121.3, 121.8, 122.6, 128.5, 128.7, 136.0, 138.9, 139.2, 153.9, 169.9. - **IR:** ν = 3278, 3204, 2727, 1670, 1625, 1589, 1553, 1500, 1310, 1233, 1134, 1088, 1047, 840. - $C_{20}H_{25}N_3O_3$ (355.43): calcd. C 67.58; H 7.09; N 11.82; found C 67.44, H 7.16, N 12.11.

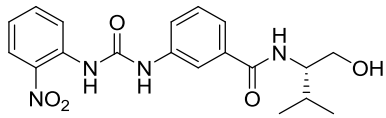
(*R*)-*N*-(2-hydroxy-1-phenylethyl)-3-(3-phenylureido)benzamide (**58o**)



According to the general procedure product **58o** was yielded as white solid (0.420 g, 1.12 mmol, 98%) starting from acid **54g** (0.320 g, 1.25 mmol) and coupled with (*R*)-2-amino-2-phenylethanol.

R*f* = 0.39 (DCM/MeOH 95:5). - m.p. 112-113°C - $[\alpha]^{20}_{D}$ = -46.89 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 3.87 (d, 2H, *J*= 6.6 Hz), 5.21 (t, 1H, *J*= 6.6 Hz), 7.02 (t, 1H, *J*= 7.3 Hz), 7.23-7.45 (m, 10H), 7.51 (d, 1H, *J*= 7.7 Hz), 7.58 (dd, 1H, *J*= 8.0, 1.1 Hz), 7.90 (s, 1H). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 56.4, 64.7, 118.0, 119.1, 121.3, 122.0, 122.6, 126.6, 127.0, 128.1, 128.5, 128.7, 135.3, 138.9, 139.4, 139.9, 153.9, 168.9. - **IR:** ν = 3300, 3205, 2727, 1646, 1621, 1599, 1563, 1348, 1298, 1235, 1175, 1065, 844. - $C_{22}H_{21}N_3O_3$ (375.42): calcd. C 70.38; H 5.64; N 11.19; found C 70.37, H 5.73, N 12.11.

(S)-N-(1-hydroxy-3-phenylpropan-2-yl)-3-(3-(2-nitrophenyl)ureido) benzamide (**58p**)

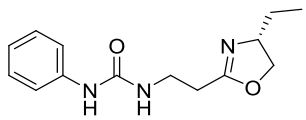


According to the general procedure product **58p** was yielded as yellow solid (0.568 g, 1.47 mmol, 97%) starting from acid **54h** (0.500 g, 1.66 mmol) and coupled with L-Valinol.
R*f* = 0.36 (DCM/MeOH 95:5). - m.p. 140-141°C - $[\alpha]^{20}_{D}$ = -47.64 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 1.00 (d, 1H, *J*= 6.8 Hz), 1.03 (d, 1H, *J*= 6.8 Hz), 2.01 (m, 1H), 3.71 (m, 2H), 3.92 (m, 1H), 7.19 (ddd, 1H, *J*= 8.4, 7.4, 1.3), 7.42 (t, 1H, *J*= 7.8 Hz), 7.51 (dt, 1H, *J*= 7.8, 1.3 Hz), 7.67 (m, 2H), 7.97 (t, 1H, *J*= 1.8 Hz), 8.19 (dd, 1H, *J*= 8.4, 1.4 Hz), 8.48 (dd, 1H, *J*= 8.6, 1.2 Hz). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 17.8, 18.7, 28.9, 57.4, 61.7, 118.2, 121.6, 122.0, 122.3, 125.2, 128.7, 134.7, 135.2, 135.8, 153.2, 169.2. - **IR:** ν = 3296, 3205, 1722, 1697, 1628, 1604, 1565, 1340, 1252, 1194, 1141, 1074, 1028, 846. - $C_{19}H_{22}N_4O_5$ (355.43): calcd. C 59.06; H 5.74; N 14.50; found C 59.27, H 6.09, 14.83.

1.10.3 General procedure for the cyclization of compounds 58 into the oxazolines Ox

Peptidic precursor **58** (1.0 equiv) was dissolved in THF (0.1M solution) and cooled at -78°C; then DAST (2.2 equiv) was added dropwise and the reaction stirred at the same temperature for 90 minutes. The mixture was filtered and the solvent evaporated under reduced pressure. The product was purified by flash chromatography eluting with MeOH (gradient from 1 to 5%) in DCM.

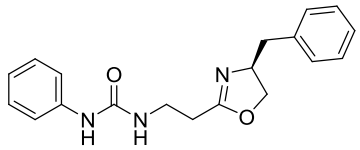
(*R*)-1-(2-(4-ethyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (**Ox-1**)



According to the general procedure product **Ox-1** was yielded as pale yellow solid (0.410 g, 1.57 mmol, 77%) starting from precursor **58a** (0.570 g, 2.04 mmol).
R*f* = 0.57 (DCM/MeOH 95:5). - m.p. 68-69°C - $[\alpha]^{20}_{D}$ = +29. 07 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, $CHCl_3$, 25°C): δ = 0.91(t, 3H, *J*= 7.3 Hz), 1.56 (m, 1H), 1.67 (m, 1H), 2.69 (t, 1H, *J*= 5.6 Hz), 3.57 (m, 2H), 4.06-4.20 (m, 2H), 4.63 (t, 1H, *J*= 8.8 Hz), 6.38 (bs, 1H), 7.02 (t, 1H, *J*= 7.7 Hz), 7.25 (m, 2H), 7.39 (d, 2H, *J*= 7.3 Hz), 7.75 (bs, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ= 9.8, 24.0, 36.5, 37.3, 53.6, 64.6, 119.6, 122.8, 128.9, 139.2, 156.8,

173.0. - **IR:** ν = 3321, 2725, 1640, 1556, 1309, 1243, 1156, 1070. - $C_{14}H_{19}N_3O_2$ (261.32): calcd. C 64.35; H 7.33; N 16.08; found C 64.44, H 7.43, N 15.41.

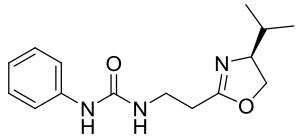
(*S*)-1-(2-(4-benzyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (**Ox-2**)



According to the general procedure product **Ox-2** was yielded as pale yellow solid (0.175g, 0.541mmol, 53%) starting from precursor **58b** (0.350 g, 1.03 mmol).

R*f* = 0.51 (DCM/MeOH 95:5). - m.p. 130-131°C - $[\alpha]^{20}_D$ = -44.65 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, $CHCl_3$, 25°C): δ = 2.44 (t, 2H, *J*= 5.8 Hz), 2.64 (dd, 1H, *J*= 13.7, 7.8 Hz), 2.96 (dd, 1H, *J*= 13.7, 5.6 Hz), 3.43-3.62 (m, 2H), 3.98 (t, 1H, *J*= 7.4 Hz), 4.20 (t, 1H, 8.4 Hz), 4.29 (m, 1H), 6.06 (bs, 1H), 7.03 (t, 1H, *J*= 7.3 Hz), 7.13 (m, 2H), 7.16-7.40 (m, 8H), 7.63 (bs, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ = 28.8, 36.6, 41.6, 66.7, 71.9, 120.5, 123.3, 126.6, 128.6, 129.1, 129.2, 137.7, 139.0, 156.2, 167.4. - **IR:** ν = 3331, 2724, 1679, 1632, 1595, 1565, 1497, 1444, 1349, 1311, 1242, 1191, 1084, 975, 924. - $C_{19}H_{21}N_3O_2$ (323.39): calcd. C 70.57; H 6.55; N 12.99; found C 70.78, H 6.32, N 13.04.

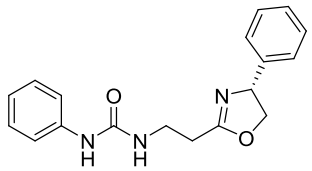
(*S*)-1-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (**Ox-3**)



According to the general procedure product **Ox-3** was yielded as white solid (0.519g, 1.88mmol, 99%) starting from precursor **58c** (0.560 g, 1.91 mmol)

R*f* = 0.59 (DCM/MeOH 95:5). - m.p. 81-81°C - $[\alpha]^{20}_D$ = -29.80 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 0.89 (d, 3H, *J*= 6.8 Hz), 0.94 (d, 3H, *J*= 6.7 Hz), 1.74 (m, 1H), 2.52 (m, 2H), 3.49 (m, 2H), 3.91 (m, 1H), 4.07 (t, 1H, *J*= 7.9 Hz), 4.31 (dd, 1H, *J*= 9.8, 8.7 Hz), 6.97 (m, 1H), 7.24 (m, 2H), 7.33 (dd, 2H, *J*= 8.7, 1.2 Hz). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 17.4, 18.6, 28.6, 36.1, 36.2, 56.6, 61.8, 118.8, 122, 128.4, 139.5, 156.8, 172.8. - **IR:** ν = 3205, 2728, 1694, 1639, 1594, 1527, 1380, 1353, 1168, 1077, 1029, 920, 832. - $C_{15}H_{21}N_3O_2$ (273.35): calcd. C 65.43; H 7.69; N 15.26; found C 65.61, H 7.99, 14.61.

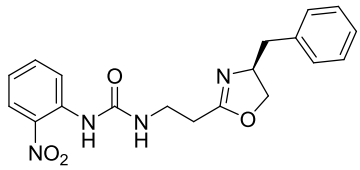
(R)-1-phenyl-3-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)ethyl)urea (**Ox-4**)



According to the general procedure product **Ox-4** was yielded white solid (0.257g, 0.83 mmol, 77%) starting from precursor **58d** (0.500 g, 1.54 mmol).

R*f* = 0.59 (DCM/MeOH 95:5). - m.p. 122-123°C - $[\alpha]^{20}_{D}$ = +38.08 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, $CHCl_3$, 25°C): δ = 2.51 (t, 2H, *J*= 5.8 Hz), 3.54 (m, 2H), 4.06 (t, 1H, *J*= 8.3 Hz), 4.56 (dd, 1H, *J*= 10.1, 8.6 Hz), 5.09 (t, 1H, *J*= 9.2 Hz), 6.18 (t, 1H, *J*= 6.0 Hz), 6.97 (m, 1H), 7.13-7.36 (m, 10H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ= 28.9, 36.6, 67.7, 69.4, 120.1, 122.9, 127.8, 128.8, 129.0, 139.1, 141.8, 156.4, 171.8 - **IR:** ν = 3310, 2726, 1678, 1620, 1567, 1541, 1310, 1245, 1180, 1076, 978, 845. - $C_{18}H_{19}N_3O_2$ (309.36): calcd. C 69.88; H 6.12; N 13.58; found C 69.58, H 6.34, N 13.89.

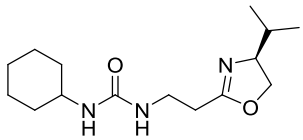
(*S*)-1-(2-(4-benzyl-4,5-dihydrooxazol-2-yl)ethyl)-3-(2-nitrophenyl)urea (**Ox-5**)



According to the general procedure product **Ox-5** was yielded as yellow solid (0.101g, 0.274mmol, 50%) starting from precursor **58e** (0.210 g, 0.543 mmol).

R*f* = 0.34 (DCM/MeOH 95:5). - m.p. 154-155°C - $[\alpha]^{20}_{D}$ = -42.12 (c = 0.1, CHCl3) - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 2.56 (t, 2H, *J*= 5.7 Hz), 2.78 (dd, 1H, *J*= 13.7, 7.9 Hz), 3.08 (dd, 1H, *J*= 13.7, 5.4 Hz), 3.61 (m, 2H), 4.10 (dd, 1H, J= 8.3, 7.4 Hz), 4.33 (t, 1H, *J*= 8.9 Hz), 4.49 (m, 1H), 6.17 (bs, 1H), 7.04 (m, 1H), 7.20-7.35 (m, 5H), 7.58 (ddd, 1H, *J*= 8.7, 7.3, 1.6 Hz), 8.16 (dd, 1H, *J*= 8.4, 1.5 Hz), 8.58 (d, 1H, *J*= 8.6 Hz), 9.72 (s, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ= 28.1, 36.6, 41.5, 66.6, 71.9, 121.3, 121.5, 125.7, 126.7, 128.6, 129.3, 134.7, 135.8, 137.0, 137.4, 153.9, 172.2. - **IR:** ν = 3353, 2724, 1651, 1613, 1543, 1309, 1264, 1140, 1104, 794. - $C_{19}H_{20}N_4O_4$ (368.38): calcd. C 61.95 ; H 5.47, N 15.21; found C 61.66, H 5.78, N 14.99.

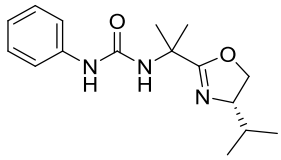
(*S*)-1-cyclohexyl-3-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)ethyl)urea (**Ox-6**)



According to the general procedure product **Ox-6** was yielded as white solid (0.402 g, 1.42 mmol, 62%) starting from precursor **58f** (0.688 g, 2.30 mmol).

R*f* = 0.54 (DCM/MeOH 95:5). - m.p. 103-104°C - $[\alpha]^{20}_{D}$ = -39.45 (c = 0.1, CHCl3) - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 0.90 (d, 3H, *J*= 6.8 Hz), 0.98 (d, 3H, *J*= 6.8 Hz), 1.08-1.39 (m, 6H), 1.59 (dt, 1H, *J*= 12.8, 3.8 Hz), 1.71 (m, 2H), 1.77 (m, 1H), 1.92 (m, 2H), 2.50 (m, 2H), 3.51 (m, 2H), 3.92 (m, 1H), 4.02 (t, 1H, *J*= 8.1 Hz), 4.32 (dd, 1H, *J*= 9.5, 8.5 Hz), 4.61 (d, 1H, J= 7.5 Hz), 5.49 (bs, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ= 18.1, 18.7, 24.9, 25.6, 28.6, 32.5, 33.9, 36.6, 49.4, 70.3, 71.3, 157.6, 167.4. - **IR:** ν = 3351, 3305, 2350, 1669, 1624, 1579, 1532, 1309, 1251, 1167, 1082, 982, 939, 891, 791. - $C_{15}H_{27}N_3O_2$ (281.39): calcd. C 64.02 ; H 9.67, N 14.93; found C 63.89, H 9.90, N 14.79.

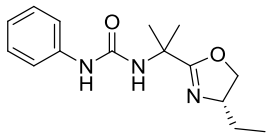
(*S*)-1-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-3-phenylurea (**Ox-7**)



According to the general procedure product **Ox-7** was yielded as white solid (0.501 g, 1.73 mmol, 84%) starting from precursor **58g** (0.635 g, 2.06 mmol).

R*f* = 0.50 (DCM/MeOH 95:5). - m.p. 189-190°C - $[\alpha]^{20}_{D}$ = -43.12 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 0.89 (d, 3H, *J*= 6.7 Hz), 0.95 (d, 3H, *J*= 6.8 Hz), 1.56 (s, 3H), 1.59 (s, 3H), 1.82 (m, 1H), 4.00 (ddd, 1H, *J*= 9.8, 7.2, 5.5 Hz), 4.12 (dd, 1H, *J*= 8.6, 7.2 Hz), 4.32 (dd, 1H, *J*= 9.8, 8.6 Hz), 6.96 (m, 1H), 7.23 (dd, 2H, *J*= 8.6, 7.5 Hz), 7.31 (dd, 2H, *J*= 8.6, 1.2). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 16.4, 17.5, 25.5, 25.7, 31.9, 51.5, 70.0, 71.2, 118.6, 121.9, 128.9, 139.4, 155.5, 172.2. - **IR:** ν = 3338, 2725, 1646, 1600, 1557, 1543, 1310, 1264, 1152, 1071, 800. - $C_{16}H_{23}N_3O_2$ (289.37): calcd. C 66.41; H 8.01, N 14.52; found C 66.53, H 8.11, 14.77.

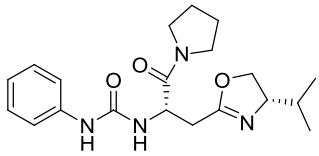
(*S*)-1-(2-(4-ethyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-3-phenylurea (**Ox-8**)



According to the general procedure product **Ox-8** was yielded as white solid (0.441 g, 1.60 mmol, 74%) starting from precursor **58h** (0.636 g, 2.17 mmol).

R*f* = 0.49 (DCM/MeOH 95:5). - m.p. 122-123°C - $[\alpha]^{20}_{D}$ = +40.82 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 0.94 (t, 3H, *J*= 7.3 Hz), 1.55 (s, 3H), 1.56 (m, 1H), 1.57 (s, 3H), 1.66 (m, 1H), 4.01 (t, 1H, *J*= 7.6 Hz), 4.08 (m, 1H), 4.39 (dd, 1H, *J*= 9.0, 7.8 Hz), 6.96 (t, 1H, *J*= 7.3 Hz), 7. 23 (t, 2H, *J*= 7.9 Hz), 7.30 (dd, 2H, *J*= 8.8, 1.2 Hz). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 8.3 25.5, 25.6, 27.6, 51.3, 66.8, 72.3, 118.6, 122.0, 128.3, 139.3, 155.4, 172.2. - **IR:** ν = 3321, 2725, 1661, 1641, 1596, 1587, 1500, 1302, 1250, 1218, 1132, 1082, 1068, 979, 955, 924, 843. - $C_{15}H_{21}N_3O_2$ (275.35): calcd. C 65.43; H 7.69, N 15.26; found C 65.57, H 7.66, N 15.37.

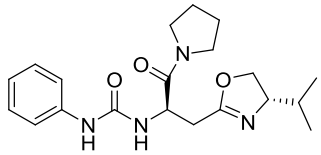
1-((*S*)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1-oxo-1-(pyrrolidin-1-yl) propan-2-yl)-3-phenylurea (**Ox-9**)



According to the general procedure product **Ox-9** was yielded as yellow solid (0.083 g, 0.22 mmol, 58%) starting from precursor **58i** (0.150 g, 0.38 mmol).

R*f* = 0.43 (DCM/MeOH 95:5). - m.p. 122-123°C - $[\alpha]^{20}_{D}$ = -71.70 (c = 0.1, CHCl3) - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 0.84 (d, 3H, *J*= 6.7 Hz), 0.92 (d, 3H, *J*= 6.7 Hz), 1.66 m, 1H), 1.87 (m, 2H), 1.96 (m, 2H), 2.68 (dd, 1H, *J*= 15.2, 6.4 Hz), 2.82 (dd, 1H, *J*= 15.2, 8.0 Hz), 3.49 (m, 2H), 3.78-3.92 (m, 4H), 4.20 (dd, 1H, *J*= 9.4, 8.2 Hz), 5.20 (m, 1H), 6.88-6.96 (m, 2H), 7.22 (t, 2H, *J*= 7.6 Hz), 7.36 (d, 2H, *J*= 7.6 Hz), 8.26 (s, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ= 18.3, 18.7, 24.3, 25.9, 31.8, 32,6, 46.3, 47.1, 48.3, 70.3, 72.2, 118.8, 122.1, 128.7, 139.6, 155.2, 163.7, 170.9. - **IR:** ν = 3330, 3223, 2721, 1656, 1623, 1567, 1504, 1398, 1311, 1214, 1200, 1178, 1123, 1083, 1034, 970. - $C_{20}H_{28}N_4O_3$ (372.46): calcd. C 64.49; H 7.58, N 15.04; found C 64.67, H 7.30, N 14.99.

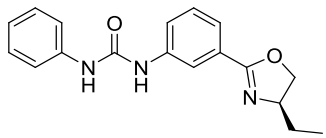
1-((*R*)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1-oxo-1-(pyrrolidin-1-yl) propan-2-yl)-3-phenylurea (**Ox-10**)



According to the general procedure product **Ox-10** was yielded as yellow solid (0.074 g, 0.20 mmol, 58%) starting from precursor **58j** (0.134 g, 0.34 mmol).

R*f* = 0.43 (DCM/MeOH 95:5). - m.p. 126-127°C - $[\alpha]^{20}_{D}$ = -13.76 (c = 0.1, CHCl3) - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 0.83 (d, 3H, *J*= 6.7 Hz), 0.87 (d, 3H, *J*= 6.7 Hz), 1.65 (m, 1H), 1.88 (m, 2H), 1.97 (m, 2H), 2.67 (dd, 1H, *J*= 15.6, 6.6 Hz), 2.81 (dd, 1H, *J*= 15.6, 8.3 Hz), 3.42-3.55 (m, 2H), 3.83-3.93 (m, 4H), 4.19 (dd, 1H, *J*= 8.7, 7.9 Hz), 5.23 (m, 1H), 6.89 (d, 1H, *J*= 9.5 Hz), 6.94 (t, 1H, *J*= 7.3 Hz), 7.21 (t, 2H, *J*= 7.7 Hz), 7.35 (d, 2H, 7.8 Hz), 8.35 (s, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ= 18.2, 18.4, 24.3, 25.9, 31.9, 32.4, 46.3, 47.1, 48.0, 70.2, 72.1, 118.8, 122.0, 128.7, 139.8, 155.1, 163.9, 171.0. - **IR:** ν = 3312, 2729, 1678, 1634, 1603, 1593, 1549, 1334, 1212, 1150, 1115, 1084, 1065, 991, 840. - $C_{20}H_{28}N_4O_3$ (372.46): calcd. C 64.49 ; H 7.58, N 15.04; found C 64.71, H 7.44, N 14.81.

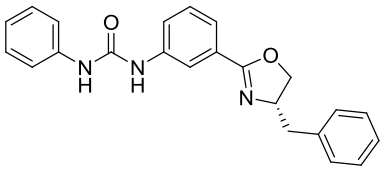
(*R*)-1-(3-(4-ethyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (**Ox-11**)



According to the general procedure product **Ox-11** was yielded as white solid (0.370 g, 1.20 mmol, 78%) starting from precursor **58k** (0.500 g, 1.53 mmol).

R*f* = 0.46 (DCM/MeOH 95:5). - m.p. 147-148°C - $[\alpha]^{20}_{D}$ = +43.30 (c = 0.1, CHCl3) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 0.99 (t, 3H, *J*= 7.3 Hz), 1.63 (m, 1H), 1.74 (m, 1H), 4.14 (t, 1H, *J*= 7.7 Hz), 4.24 (m, 1H), 4.54 (dd, 1H, *J*= 9.4, 8.2 Hz), 7.02 (m, 1H), 7.29 (m, 2H), 7.37 (t, 1H, *J*= 8.2 Hz), 7.43 (dd, 2H, *J*= 8.7, 1.1 Hz), 7.58 (dt, 1H, *J*= 7.7, 1.3 Hz), 7.68 (ddd, 1H, *J*= 8.1, 2.3, 1.0 Hz), 7,96 (t, 1H, *J*= 2.0 Hz).). - **^{13}C NMR** (100.6 MHz, CD_3OD, 25°C): δ= 8.52, 28.0, 67.1, 72.0, 118.4, 119.0, 122.1, 122.6, 127.8, 128.5, 128,7, 138.9, 139.6, 153.8, 164.6. - **IR:** ν = 3309, 3281, 1644, 1612, 1592, 1572, 1448, 1311, 1298, 1237, 1168, 1080, 1059, 973, 926. - $C_{18}H_{19}N_3O_2$ (309.36): calcd. C 69.98; H 6.19, N 13.58; found C 70.01, H 6.15, N 13.54.

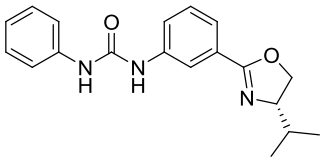
(*S*)-1-(3-(4-benzyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (**Ox-12**)



According to the general procedure product **Ox-12** was yielded as white solid (0.518 g, 1.39 mmol, 78%) starting from precursor **58l** (0.693 g, 1.78 mmol).

R*f* = 0.52 (DCM/MeOH 95:5). - m.p. 106-107°C - $[\alpha]^{20}_{D}$ = -37.89 (c = 0.1, $CHCl_3$) - **^{1}H NMR** (400 MHz, $CHCl_3$, 25°C): δ = 2.64 (dd, 1H, *J*= 13.7, 9.0 Hz), 3.12 (dd, 1H, *J*= 13.7, 5.1 Hz), 4.02 (t, 1H, *J*= 7.8 Hz), 4.22 (t, 1H, *J*= 8.8 Hz), 4.47 (m, 1H), 6.95 (t, 1H, *J*= 7.1 Hz), 7.11-7.27 (m, 11H), 7.54 (d, 1H, *J*= 7.1 Hz), 7.94 (d, 2H, *J*= 8.1 Hz), 8.04 (s, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ=41.8, 67.6, 72.0, 119.8, 120.5, 123.0, 123.1, 123.6, 126.6, 128.1, 128.6, 128.9, 129.0, 129.1, 137.8, 138.2, 138.7, 154.0, 164.4. - **IR:** ν = 3353, 2724, 2360, 1649, 1597, 1555, 1310, 1264, 1201, 1154, 1074, 896, 845. - $C_{23}H_{21}N_3O_2$ (371.43): calcd. C 74.37 ; H 5.70, N 11.31; found C 77.37, H 5.68, N 10.95.

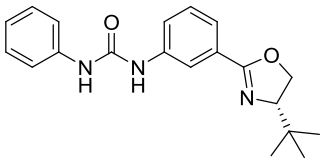
(*S*)-1-(3-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (**Ox-13**)



According to the general procedure product **Ox-13** was yielded as white solid (0.458 g, 1.42 mmol, 91%) starting from precursor **58m** (0.530 g, 1.55 mmol).

R*f* = 0.49 (DCM/MeOH 95:5). - m.p. 138-139°C - $[\alpha]^{20}_{D}$ = -35.05 (c = 0.1, CHCl3) - **^{1}H NMR** (400 MHz, CD_2Cl_2, 25°C): δ = 0.92 (d, 3H, *J*= 6.8 Hz), 1.01 (d, 3H, *J*= 6.7 Hz), 1.84 (m, 1H), 2.15 (bs, 1H), 4.09 (ddd, 1H, *J*= 9.5, 8.2, 6.4 Hz), 4.16 (t, 1H, 8.2 Hz), 4.43 (dd, 1H, J= 9.5, 8.3 Hz), 7.10 (m, 1H), 7.14 (bs, 1H), 7.25 (bs, 1H), 7.28-7.37 (m, 5H), 7.50 (ddd, 1H, *J*= 8.0, 2.1, 0.9 Hz), 7.60 (dt, 1H, J= 7.7, 1.1 Hz), 7.95 (t, 1H, *J*= 1.7 Hz). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ= 17.6, 18.8, 32.4, 70.6, 71.2, 119.4, 120.8, 123.2, 123.6, 123.9, 128.9, 129.1, 129.3, 138.0, 138.8, 139.0, 153.6, 165.0. - **IR:** ν = 3319, 2725, 1743, 1646, 1595, 1567, 1309, 1262, 1155, 1069, 801. - $C_{19}H_{21}N_3O_2$ (323.39): calcd. C 70.57; H 6.55, N 12.99; found C 70.19, H 6.41, N 12.83.

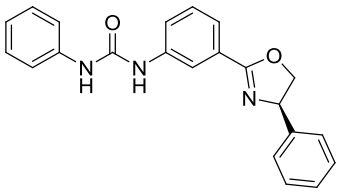
(*S*)-1-(3-(4-tert-butyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (**Ox-14**)



According to the general procedure product **Ox-14** was yielded as white solid (0.436 g, 1.29 mmol, 83%) starting from precursor **58n** (0.552 g, 1.55 mmol).

R*f* = 0.48 (DCM/MeOH 95:5). - m.p. 170-171°C - $[\alpha]^{20}_{D}$ = -47.13 (c = 0.1, CHCl3) - **^{1}H NMR** (400 MHz, CD_3OD, 25°C): δ = 1.02 (s, 9H), 3.63 (dd, 1H, *J*= 11.5, 8.9 Hz), 3.88 (dd, 1H, *J*= 11.5, 3.4 Hz), 4.04 (dd, 1H, *J*= 8.9, 3.4 Hz), 7.03 (t, 1H, *J*= 7.4 Hz), 7.30 (dd, 2H, *J*= 8.4, 7.4 Hz), 7.40 (t, 1H, *J*= 7.7 Hz), 7.44 (m, 2H), 7.48 (ddd, 1H, *J*= 7.7, 1.7, 1.1 Hz), 7.59 (ddd, 1H, *J*= 8.2, 2.2, 1.1 Hz), 7.82 (t, 1H, *J*= 1.7 Hz) - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ= 25.8, 33.9, 68.8, 75.9, 119.8, 120.6, 123.0, 123.1, 123.6, 128.3,129.0, 138.1, 138.6, 154.0, 163.7. - **IR:** ν = 3352, 2724, 2360, 1740, 1647, 1596, 1560, 1309, 1264, 1204, 1154, 1073, 897, 799. - $C_{20}H_{23}N_3O_2$ (337.42): calcd. C 71.19 ; H 6.87, N 12.45; found C 71.44, H 7.10, N 12.47.

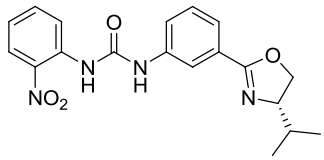
(*R*)-1-phenyl-3-(3-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)urea (**Ox-15**)



According to the general procedure product **Ox-15** was yielded as white solid (0.103 g, 0.29 mmol, 30%) starting from precursor **58o** (0.400 g, 1.06 mmol).

R*f* = 0.45 (DCM/MeOH 95:5). - m.p. 134-135°C - $[\alpha]^{20}_{D}$ = -51.78 (c = 0.1, CHCl3) - **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ = 4.25 (t, 1H, *J*= 8.3 Hz), 4.90 (dd, 1H, *J*= 10.1, 8.3 Hz), 5.45 (dd, 1H, *J*= 10.1, 8.3 Hz), 6.98 (t, 1H *J*= 7.3 Hz), 7.24-7.31 (m, 3H), 7,34-7.41 (m, 5H), 7.55 (dd, 2H, *J*= 8.7, 1.1 Hz), 7.65 (dt, 1H, *J*= 7.7, 1.3 Hz), 7.73 (ddd, 1H, *J*= 8.2, 2.3, 1.1 Hz), 8.23 (t, 1H, *J*= 1.9 Hz), 8.36 (s, 1H), 8.52 (s, 1H). - **^{13}C NMR** (100.6 MHz, $CDCl_3$, 25°C): δ= 69.5, 74.9, 118.2, 118.5, 118.6, 121.5, 121.6, 121.9, 122.1, 126.7, 127.3, 128.1, 128.5, 128.7, 128.9, 139.9, 140.4, 142.9, 152.5, 164.3. - **IR:** ν = 3321, 3278, 2725, 1709, 1656, 1611, 1561, 1311, 1223, 1189, 1063, 970, 840. - $C_{22}H_{19}N_3O_2$ (357.41): calcd. C 73.93 ; H 5.36, N 11.76; found C 73.57, H 5.63, N 11.46.

(*S*)-1-(3-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-3-(2-nitrophenyl)urea (**Ox-16**)



According to the general procedure product **Ox-16** was yielded as yellow solid (0.441 g, 1.20 mmol, 82%) starting from precursor **58p** (0.565 g, 1.46 mmol).

R*f* = 0.38 (DCM/MeOH 95:5). - m.p. 166-167°C - $[\alpha]^{20}_{D}$ = -49.37 (c = 0.1, CHCl3) - **^{1}H NMR** (400 MHz, CD_2Cl_2, 25°C): δ = (d, 3H, *J*= 6.7 Hz), 1.05 (d, 3H, *J*= 6.7 Hz), 1.84 (m, 1H), 4.07-4.18 (m, 2H), 4.45 (dd, 1H, *J*= 9.2, 7.8 Hz), 7.10 (bs, 1H), 7.15 (ddd, 1H, *J*= 8.4, 7.2, 1.3 Hz), 7.43 (t, 1H, *J*= 7.7 Hz), 7.64 (ddd, 1H, *J*= 7.9, 2.1, 1.0 Hz), 7.68 (ddd, 1H, *J*= 8.7, 7.1, 1.6 Hz), 7.72 (dt, 1H, *J*= 7.7, 1.2 Hz), 8.04 (t, 1H, *J*= 2.0 Hz), 8.22 (dd, 1H, *J*= 8.6, 1.6 Hz), 8.68 (dd, 1H, *J*= 8.7, 1.1 Hz), 9.94 (bs, 1H). - **^{13}C NMR** (100.6 MHz, CH_2Cl_2, 25°C): δ= 17.8, 18.6, 32.8, 70.3, 72.5, 119.7, 121.9, 122.1,122.9, 123.4, 125.5, 128.8, 129.1, 135.4, 136.0, 136.7, 138.4, 151.8, 163.1. - **IR:** ν = 3339, 3281, 2724, 1650, 1591, 1557, 1309, 1278, 1155, 1066, 823. - $C_{19}H_{20}N_4O_4$ (368.39): calcd. C 61.95; H 5.47, N 15.21; found C 61.71, H 5.84, N 13.47.

1.10.4 Characterization of metal complexes

Yoe-Jones plot

$CuCl_2$ (2 mg, 0.015 mmol) were transferred in a glass cuvette and 3 mL CH_2Cl_2 were added.
A stock solution of (S)-1-(3-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (**Ox-13**) (11.52 mg, 0.036 mmol) in 0.5 mL of CH_2Cl_2 and 15µL of MeOH was prepared and then sequentially added in accurately portions with the use of a micropipette up to 2.4 equivalents of ligand, performing UV absorption spectrum after each addition.
UV absorption value at 741 nm (λ_{max}) and the different Ligand/Metal ratio, were plotted in a 2D graph.

$CuCl_2$ (4 mg, 0.030 mmol) were transferred in a glass cuvette and 3 mL CH_2Cl_2 were added.
A stock solution of (S)-4-isopropyl-2-phenyl-4,5-dihydrooxazole (**Ox-0**) (12.60 mg, 0.078 mmol) in 0.5 mL of CH_2Cl_2 was prepared and then sequentially added in accurately portions

with the use of a micropipette up to 2.6 equivalents of ligand, performing UV absorption spectrum after each addition.
UV absorption value at 757 nm (λ_{max}) and the different Ligand/Metal ratio, were plotted in a 2D graph.

Dilution studies - NMR evaluations

(S)-1-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (**Ox-3**) (100mg, 0.363 mmol) and $PdCl_2(CH_3CN)_2$ (47mg, 0.181mmol) were dissolved in 5mL DCM and stirred for 1 hour at room temperature. Complex was achieved by precipitation with hexane.
^{1}H NMR experiments were carried out focusing on the variation of chemical shift of the NH signals upon different concentrations (5, 10, 20 and 40 mM) both in the complex and in the free ligand.

1.10.5 General procedure for the asymmetric Friedel-Crafts alkylation of 1H-indole with dimethyl-2-benzylidenemalonate

$Cu(OTf)_2$ (0.05 equiv.) and the ligand (0.1 equiv.) were dissolved in the solvent (0.1 M solution respect the substrate) and stirred at room temperature for 2 hours. Dimethyl-2-benzylidenemalonate **59** (1.0 equiv.) was added and the solution was then cooled down to 15°C. The reaction was stirred for 30 min at 15°C, then added the 1H-indole **60** (1.5 equiv.) and stirred maintaining the temperature at 15°C.
After the reaction was complete (monitored by TLC), the solvent was removed under vacuum and the residue was chromatographed on silica gel column with Petroleum ether/Ethyl acetate 5:1 to afford the final product.
Spectroscopical data of products were in agreement with the literature[95] and enantiomeric excesses were determined by HPLC equipped with chiral column Chiracel OD-H.

[95] Y-J. Sun, N. Li, Z-B. Zheng, L. Liu, Y-B. Yu, Z-H. Qin, B. Fua, *Adv. Synth. Catal*. **2009**, *351*, 3113.

1.10.6 General procedure for the asymmetric Friedel-Crafts alkylation of 1H-indole with *trans*-β-nitrostyrene

$Zn(OTf)_2$ (0.05 equiv.) and the ligand (0.1 equiv.) were dissolved in the solvent (0.1 M solution respect the substrate) and stirred at room temperature for 2 hours. *Trans*-β-nitrostyrene **62** (1.5 equiv.) was added and then the solution was cooled down (to 15°C or 0°C). The reaction was stirred for 30 min at the same temperature (15°C or 0°C), then added the 1H-indole **60** (1.0 equiv.) and finally stirred maintaining the temperature (15°C or 0°C).
After the reaction was complete (monitored by TLC), the solvent was removed under vacuum and the residue was chromatographed on silica gel column with Petroleum ether/Ethyl acetate 3:1 to afford the final product.
Spectroscopical data of products were in agreement with the literature[96] and enantiomeric excesses were determined by HPLC equipped with chiral column Chiracel OD-H.

1.10.7 General procedure for kinetic resolution of 1,2-hydrobenzoin

Ligand (0.1 equiv.) was solved in CH_2Cl_2 (0.15 M solution respect the substrate) and $CuCl_2$ (0.05 equiv.) added and mixture stirred until the solution became clear and then cooled at 0°C. Substrate **64** (1.0 equiv.), diisopropylethylamine (1.0 equiv.) and acyl chloride (0.5 equiv.) were added and the reaction stirred for 3 hours at 0°C. The reaction mixture was filtered on silica gel washing with CH_2Cl_2 and the solvent evaporated under reduced pressure. Monobenzoylated **65** product was purified by flash chromatography on silica gel eluting with Hexane/Ethyl acetate 3:1. Spectroscopical data of products were in agreement with the literature[97] and enantiomeric excesses were determined by HPLC equipped with chiral column Chiralpak AS-H .

1.10.8 General procedure for selective desymmetrization of *meso*-1,2-hydrobenzoin

Ligand (0.1 equiv.) was solved in CH_2Cl_2 (0.15 M solution respect the substrate) and $CuCl_2$ (0.05 equiv.) added and the mixture stirred until the solution became clear and then cooled at 0°C. Substrate **66** (1.0 equiv.), diisopropylethylamine (1.0 equiv.) and acyl chloride (1.0

[96] S-F. Lu, D-M. Du, J. Xu, *Org. Lett.* **2006**, *8*, 2115.
[97] A. Gissibl, M. G. Finn, O. Reiser, *Org. Lett.* **2005**, *7*, 2325.

equiv.) were added and the reaction stirred for 3 hours at 0°C. The reaction mixture was filtered on silica gel washing with CH_2Cl_2 and the solvent evaporated under reduced pressure. Monobenzoylated **67** product was purified by flash chromatography on silica gel eluting with Hexane/Ethyl acetate 3:1. Spectroscopical data of products were in agreement with the literature[98] and enantiomeric excesses were determined by HPLC equipped with chiral column Chiralpak AS-H.

[98] Y. Matzumura, T. Maki, S. Murakami, O. Onomura, *J. A. Chem. Soc.* **2003**, *125*, 2025.

Chapter 2

Chiral Supramolecular Phosphinooxazoline Ligands

2.1 Introduction

In the previous chapter the development of the supramolecular version of the bis(oxazoline) ligands was introduced. Bis(oxazolines) are homobidentate ligands in the sense that the two binding atoms are equal (namely two nitrogen atoms), and such bis(oxazolines) are also defined as *N*,*N*-ligands. Diphosphorus ligands are also very common (e.g. BINAP, DIOP etc.).

However, in some ligands the two binding atoms are different and these are called heterobidentate ligands. A crucial peculiarity of heterobidentate chiral ligands is that, if used in metal catalyzed asymmetric transformations, they are able to induce discrimination not just through steric factors, but also by the creation of an electronic asymmetry on the metal centre thanks to the presence of different donor atoms. The class of ligands that bear phosphorus and nitrogen as chelating atoms is the most important and widely used considering the large number of works reported in literature. These so called *P*,*N*-ligands combine the π-acceptor character of phosphorus, typically suited for stabilizing a metal centre in a low oxidation state, with the σ-donor ability of nitrogen, that makes the metal susceptible to oxidative addition reactions. These important features can play a fundamental role in stabilizing intermediate oxidation states and/or geometries during the catalytic cycle.[99] The electronic asymmetry can further be increased by playing on the nature of adjacent atoms at phosphorous and/or nitrogen. For instance, bonding the phosphorus directly to a more electronegative atom, such as oxygen or nitrogen, it lessens its electron-donating ability and in the same time enhances its π-acceptor capacity. On the contrary, the presence of an imino rather than an amino group results in a nitrogen donor atom of greater σ-donating capabilities; finally resulting in a bigger electronic disparity between the two donor atoms.

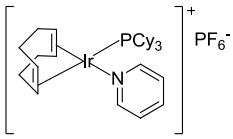
Obviously, all the features above mentioned have prompted, so far, the development of a plethora of *P*,*N*-ligands successfully applied in a wide range of reactions catalyzed by transition metal-complexes.[100]

[99] P. Espinet, K. Soulantica, *Coord. Chem. Rev.* **1999,** 499.
[100] M. Schoenleber, R. Hilgraf, A. Pfaltz, *Adv. Synth. Catal.* **2008,** *350*, 2033; S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007,** *40*, 1402.

2.2 Bidentate phosphorus-nitrogen ligands

In 1974 Hayashi and Kumada reported the application of the first bidentate chiral *P,N*-ligands.[101] In particular they developed and applied PPFA and BPPFA, two example of ferrocenyl derivatives, in the hydrosilylation of ketones. Although the optical purity was not impressive (up to 49% ee), they demonstrated the ability of these ligands to induce asymmetry.

Approximately in the same years, Crabtree showed the ability of iridium towards the coordination of one P-ligand and one N-ligand, instead of forming the corresponding homocomplexes. The achiral *P,N*-ligand iridium catalyst was developed while working on the iridium analog of Wilkinson's rhodium-based catalyst. In 1977 he reported the first application of his catalyst, $[Ir(cod)(Py)PCy_3]PF_6$ (**68**), to the hydrogenation of alkenes.[102] In the catalyst, a nitrogen atom (pyridine) and one phosphorus atom (PCy_3) were coordinated in *cis*-configuration around a square planar iridium.



68

Crabtree's catalyst immediately showed to be 100 times more active than the Wilkinson's catalyst and able to hydrogenate non-functionalized alkenes, even tri- and tetrasubstituted, unlike the rhodium catalyst.[103]

This breakthrough ended in the development by chemists of others catalysts, in particular bidentate chiral *P,N*-ligands for asymmetric applications.

What makes P,N-ligands iridium complexes particularly attractive for hydrogenation reactions is that they either do not require a polar coordinating group next to the unsatured bond, in complete contrast to rhodium and ruthenium phosphine catalysts, or that they are perfect catalysts for functionalized olefins for which no other suitable chiral catalysts are available.[104]

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[101] T. Hayashi, K. Yamamoto, M. Kumada, *Tetrahedron Lett.* **1976**, *17*, 1133.
[102] R. H. Crabtree, H. Felkin, G. E. Morris *Organomet. Chem.* **1977**, 141, 205.
[103] R. H. Crabtree, *Acc. Chem. Res.***1979**, *12*, 331.
[104] A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wüstenberg, N. Zimmermann, *Adv. Synth. Catal.* **2003**, *345*, 33; S. Bell, B. Westenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, Science **2006**, *311*, 642; S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5194;

Among the different type of *P*,*N*-ligands, mono(oxazoline)-phosphorus ligands are probably one of the most common class of ligands used in catalysis.
Since the ligands we formed belong to this category, a brief overview of this ligand class will be discussed here below.

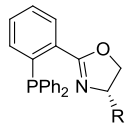
2.3 Mono(oxazoline)-Phosphorous Ligands

Up to now, complexes of these ligands showed good efficiency in several asymmetric metal-catalyzed reactions, mainly Ir-catalyzed hydrogenations of unsatured substrates (e.g. imines,[105] unfunctionalyzed olefins,[106] fluorinated olefins,[107] allylic alcohols,[108] allylic acetates,[109] enol phophinates,[110] α,β-unsatured carboxylic acids,[111] enamines.[112]) and Pd-catalyzed allylic alkylations.[113]
For convenience, hereafter the ligands will be described spoiled in categories according to the nature of phosphorous-derivatives.

2.3.1 Phosphinooxazoline Ligands

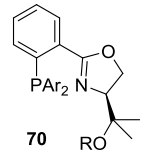
Over the last decades, mono(oxazoline)-phosphine ligands, also called phosphinooxazolines, have found a good application in metal-catalyzed asymmetric transformations. The first example of phosphinooxazoline ligand **69** was introduced by Pfaltz in 1993 as efficient ligand for allylic alkylation.[114]
The ease of accessibility of these molecules from readily available starting materials prompted the development of a wide array of phosphinooxazoline ligands similar to **69**.

M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem. Int. Ed*. **2007**, *46*, 8274; X. Li, L. Kong, Y. Gao, X. Wang, *Tetrahedron Lett.* **2007**, *48*, 3915.
[105] P. Schnider, G. Koch, Roger Prétôt, G. Wang, F. M. Bohnen, C. Krüger, A. Pfaltz, *Chem–Eur. J.* **1997**, *3*, 887; A. Franzke, F. Voss, A. Pfaltz, *Tetrahedron* **2011**, *67*, 4358.
[106] C. Hedberg, K. Källström, P. Brandt, L. K. Hansen, P. G. Andersson, *J. Am. Chem. Soc.* **2006**, *128*, 2995; S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res*, **2007**, *40*, 1402; A. Franzke, A. Pfaltz, *Chem–Eur. J*. **2011**, *17*, 4131.
[107] M. Engman, J. S. Diesen, A. Paptchikhine, P. G. Andersson, *J. Am. Chem. Soc*. **2007**, *129*, 4536.
[108] S. P. Smidt, F. Menges, A. Pfaltz, *Org. Lett.* **2004**, *6*, 2023.
[109] C. Hedberg, K. Källström, P. Brandt, L. K. Hansen, P. G. Andersson, *J. Am. Chem. Soc.* **2006**, *128*, 2995;
[110] P. Cheruku, S. Gohil, P.G. Andersson, *Org. Lett*. **2007**, *9*, 1659.
[111] S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5194; S. Li, S-F. Zhu, C-M. Zhang, S. Song, Q-L. Zhou, *J. Am. Chem. Soc*. **2008**, *130*, 8584.
[112] A. Baeza, A. Pfaltz, *Chem–Eur. J.* **2009**, *15*, 2266.
[113] D-R. Hou, J. H. Reibenspies, K. Burgess, *J. Org. Chem.* **2001**, *66*, 206; X. Zhao, D. Liu, F. Xie, Y. Liu, W. Zhang, *Org. Biomol. Chem*. **2011**, *9*, 1871.
[114] P. Matt, A. Pfaltz, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566; J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769; G. J. Dawson, C. G. Frost, S. J. Williams, *Tetrahedron Lett.* **1993**, *34*, 3149.



69

a R = Bn
b R = *i*-Pr
c R = Ph
d R = *t*-Bu
e R = Me

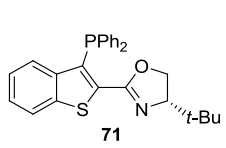


70

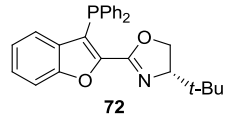
a Ar = Ph, R = Me
b Ar = Ph, R = Bn
c Ar = Ph, R = Ac
d Ar = Ph, R = Bz
e Ar = *o*Tol, R = Ac
f Ar = *o*Tol, R = Bz
g Ar = *o*Tol, R = Piv

Recently, a series of serine-based phosphinooxazoline ligands **70** was synthesized again by Pfaltz, and the corresponding iridium complexes were successfully applied in the asymmetric hydrogenation of various unfunctionalized olefines and acetophenone-N-phenyl-imine. The results showed that these new derivatives were useful substitutes for the standard *tert*-leucine-derived PHOX ligands.[115]

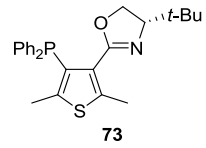
Tietze applied a large library of benzothiophene, thiophene and benzofuran phosphinooxazoline ligands **71-75** in Pd-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate with sodium dimethyl malonate with successful in terms of yield and selectivity (Scheme 2.1).[116]



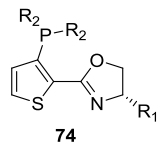
71



72

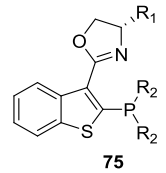


73



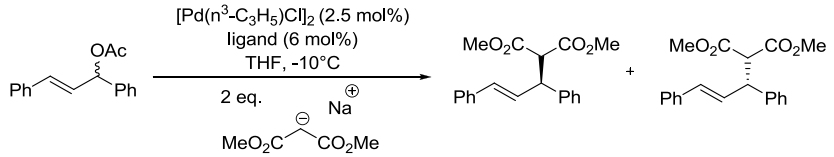
74

a R_1 = *i*-Pr, R_2 = Ph
b R_1 = *t*-Bu, R_2 = Ph
c R_1 = *t*-Bu, R_2 = *o*-Tol
d R_1 = *t*-Bu, R_2 = Cy



75

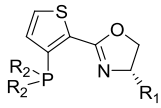
a R_1 = *i*-Pr, R_2 = Ph
b R_1 = *t*-Bu, R_2 = Ph
c R_1 = *i*-Pr, R_2 = *o*-Tol
d R_1 = Ph, R_2 = Ph



Scheme 2.1

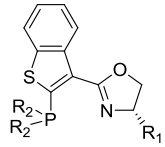
[115] A. Franzke, F. Voss, A. Pfaltz, *Tetrahedron* **2011**, 67, 4358.
[116] L. F. Tietze, J. K. Lohmann, *Synlett* **2002**, 2083.

Thiophene moiety were also used by Cozzi for the development of ligands **76** and **77,** which proved to be highly active in the iridium-catalyzed asymmetric hydrogenation of olefins and imines.[117]



76

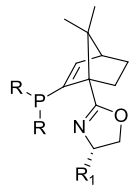
a R_1 = *i*-Pr, R_2 = Ph
b R_1 = *t*-Bu, R_2 = Ph
c R_1 = *t*-Bu, R_2 = *o*-Tol
d R_1 = *t*-Bu, R_2 = Cy



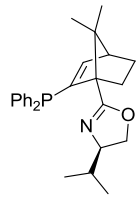
77

a R_1 = *i*-Pr, R_2 = Ph
b R_1 = *t*-Bu, R_2 = Ph
c R_1 = *i*-Pr, R_2 = *o*-Tol
d R_1 = Ph, R_2 = Ph

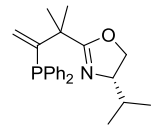
The rule of the rigidity of the linker between N and P coordination atoms was investigated by Gilbertson with the development of chiral phosphinooxazolines **78** and **79** based on (1*S*)-(+)-ketopinic acid and their application to the asymmetric Pd-catalyzed Heck reaction.[118] The two diastereomer **78b** and **79** indicated that the asymmetry of the reaction was induced by the chirality of the oxazoline, however, the low enantioselectivity obtained by the corresponding acyclic analog **80** highlighted the importance of the rigid bicyclic system for high values of enantioselection.



78



79



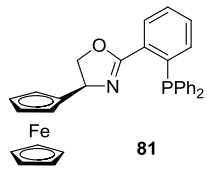
80

a R_1 = *t*-Bu, R = Ph
b R_1 = *i*-Pr, R = Ph
c R_1 = Ph, R = Ph
d R_1 = *t*-Bu, R = Cy

Ligand **81**, a ferrocenyl derivative introduced by Patti, was applied in Pd-catalyzed allylic alkylations with good results.[119]

Following this route Moyano reported an alternative synthesis of the enantiomeric ligand (*S*)-**81** and the formation of a palladium-allyl complex [(Pd(η3-C_3H_5)-**81**)PF_6] affording enantioselectivity up to 99.6% although with low catalytic activity.[120]

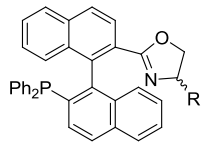
[117] P. G. Cozzi, F. Menges, S. Kaiser, *Synlett* **2003**, 833.
[118] S. R. Gilbertson, Z. Fu, *Org. Lett.* **2001**, *3*, 161.
[119] A. Patti, M. Lotz, P. Knochel, *Tetrahedron: Asymmetry* **2001**, *12*, 3375.
[120] R. M. Moreno, A. Bueno, A. Moyano, *J. Organomet. Chem.* **2002**, *660*, 62.



81

Binaphthyl moiety is a typical backbone for the synthesis of chiral ligands and, of course, it has been also used for the development of new classes of phosphinooxazolines.

Ligands **82** with an axially chirality, were used by Ikeda[121] for the Pd-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. It is very important to notice that the opposite enantioselectivity obtained by the two diastereomers **(*S*,a*R*)-82a** and **(*S*,a*S*)-82a** which indicates that the chiral binaphthyl skeleton is the more influential stereogenic unit in the structure.

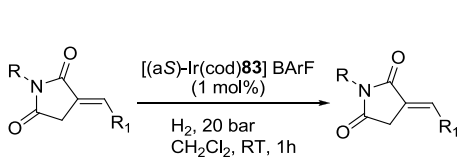


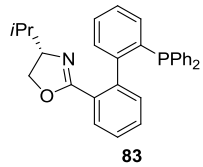
82 (***S***, a***S***) or (***S***, a***R***)

a R= *i*-Pr
b R= *t*-Bu

One of the few examples of a highly enantioselective Rh-catalyzed allylic alkylation was reported by Hayashi using ligands **82** high enantio- and regioselectivities.[122]

Another type of ligands with a stereoaxial chirality, was applied in the Ir-catalyzed hydrogenation of α-alkylidene succinimides. Ligand **83**, with a biphenyl skeleton, afforded the hydrogenated products in excellent yields (>99%) and enantioselectivities (up to 99% ee). The reactions occured with successful even with very low amount (0.05 mol%) of catalyst loading and using only 1 bar of hydrogen pressure (Scheme 2.2).[123]



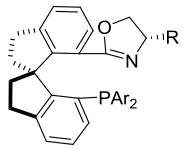


83

Scheme 2.2

[121] Y. Imai, W. Zhang, T. Kida, Y. Nakatsuji, I. Ikeda, *Tetrahedron Lett.* **1998**, *39*, 4343.
[122] T. Hayashi, A. Okada, T. Suzuka, M. Kawatsura, *Org. Lett.* **2003**, *5*, 1713.
[123] Y. Liu, W. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2203.

Zhou synthesized a wide range of spirophosphinooxazoline ligands **84**, reporting applications of the corresponding Ir-complexes to hydrogenation of alkenes,[124] and β,γ-unsaturated carboxylic acids.[125]

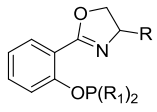


84

a Ar = Ph, R = Bn
b Ar = 3,5-$Me_2C_6H_3$, R = Bn
c Ar = 3,5-$tBu_2C_6H_3$, R = Bn
d Ar = 3,5-$tBu_2C_6H_3$, R = H
e Ar = 3,5-$tBu_2C_6H_3$, R = iPr
f Ar = 3,5-$tBu_2C_6H_3$, R = Ph

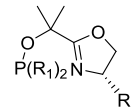
2.3.2 Oxazoline-Phosphonite Ligands

Bidentate chiral *P,N*-ligands **85** were reported by Gómez and applied in the Pd-catalyzed asymmetric allylic alkylation of 1,2-dipheylpropenyl acetate (Scheme 2.1).[126]
Pfaltz reported the application of ligands **86** to Ir-catalyzed asymmetric hydrogenation of unfuctionalized olefins with excellent results in terms of both conversion and enantioselectivity. In addition, promising results were also obtained with certain functionalized alkenes, furans and benzofurans.[127]



85

a R= Et, R_1 = Ph
b R= iPr, R_1 = Ph
c R= Et, R_1 = Cy
d R= iPr, R_1 = Cy



86

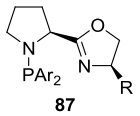
a R= tBu, R_1 = Ph
b R= tBu, R_1 = o-Tol
c R= iPr, R_1 = Ph
d R= iPr, R_1 = o-Tol

2.3.3 Oxazoline-Phosphinamine Ligands

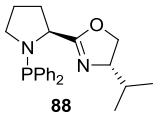
Gilbertson synthesized ligands **87-90** to study both the importance of the stereocenter in the linker and the activity of diarylphosphino groups directly bonded to a nitrogen atom.

[124] S. Song, S-F. Zhu, L-Y. Pu, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 6072; S. Song, S.-F. Zhu, Y.-B. Yu, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 1556.
[125] S. Song, S-F. Zhu, S. Yang, S. Li, Q-L. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 2708.
[126] D. Franco, M. Gómez, F. Giménez, G. Muller, M. Rocamora, M. A. Maerstro, J. Mahia, *Organometallics* **2004**, *23*, 3197.
[127] S. S. Smidt, F. Menges, A. Pfaltz, *Org. Lett.* **2004**, *6*, 2023; S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007,** *40*, 1402.

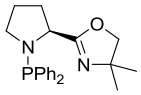
These proline-based ligands were tested in the Pd-catalyzed asymmetric alkylation and amination,[128] and in the Ir-catalyzed enantioselective hydrogenation of aromatic olefins.[129] The influence of the stereogenic proline in the asymmetric induction was demonstrated by the much lower ee% achieved with the structurally similar ligand **90** which lacks the rigidity of the pyrrolidine ring.



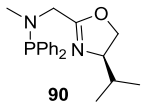
87



88



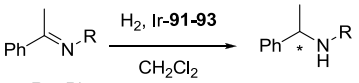
89



90

a R = Ph, Ar = Ph
b R = *i*-Pr, Ar = Ph
c R = *t*-Bu, Ar = Ph
d R = *t*-Bu, Ar = *o*-Tol
e R = *t*-Bu, Ar = 2-ethylphenyl
f R = *t*-Bu, Ar = 2,3-dimethylphenyl
g R = *t*-Bu, Ar = 2,4-dimethylphenyl

Iridium-complexes of ligands **91-93** were used in the asymmetric hydrogenation of imines by Niedercorn with high conversion and moderate to high enantiomeric excess (Scheme 2.3).[130]

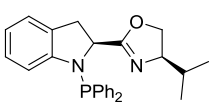


a R = Ph
b R = Bn

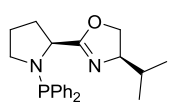
Scheme 2.3

Analogs ligands were developed by Chakka, with a family of tetrahydroisoquinoline phosphine–oxazoline **94** iridium complexes for the asymmetric hydrogenation of olefins. The best results obtained in this study showed 99% of conversions and enantiomeric excesses of up to 91%.[131]

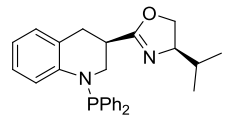
[128] G. Xu, S. R. Gilbertson, *Tetrahedron Lett.* **2002**, *43*, 2811.
[129] G. Xu, S. R. Gilbertson, *Tetrahedron Lett.* **2002**, *44*, 953.
[130] C. Blanc, F. Agbossou-Niedercorn, G. Nowogrocki, *Tetrahedron: Asymmetry* **2004**, *15*, 2159.
[131] S. K. Chakka, B. K. Peters, P. G. Andersson, G. E. M. Maguire, H. G. Kruger, T. Govender, *Tetrahedron: Asymmetry* **2010**, *21*, 2295.



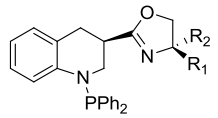
91



93



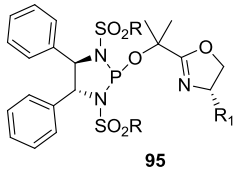
93



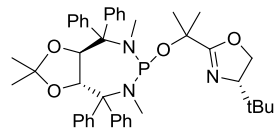
94

a R_1 = Ph, R_2 = H
b R_1 = H, R_2 = Ph
c R_1 = *i*Pr, R_2 = H
d R_1 = H, R_2 = *i*Pr

Pfaltz reported a series of oxazoline-phosphinamine ligands **95-96** containing a chiral oxazoline ring and a bis(N-sulfonylamino)phosphine group embedded in a diazaphospholidine ring or in a diazaphosphepine ring derived from TADDOL. The ligands were applied in the Pd-catalyzed allylic alkylation and Ir-catalyzed hydrogenation of methylstilene.[132] A broader library of ligands **95** was later employed for iridium-complexes in hydrogenation reactions of further unfunctionalized olefins and α,β-unsaturated carboxylic esters.[133]



95



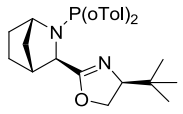
96

a R = 4-tolyl, R_1 = tBu
b R = 4-tolyl, R_1 = Ph
c R = CF_3, R_1 = tBu
d R = mesityl, R_1 = tBu
e R = 1-naphtyl, R_1 = tBu
f R = 2-naphtyl, R_1 = tBu
g R = 1-naphthylmethyl, R_1 = tBu
h R = 4-*t*Bu-C_6H_4, R_1 = tBu
i R = 4-Ph-C_6H_4, R_1 = tBu

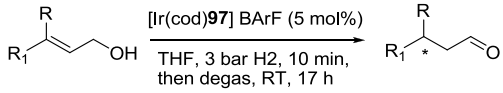
2.3.4 Oxazoline-Phosphoramidate Ligands

Andersson's group prepared iridium *N,P*-ligand complexes containing the bidentate oxazoline-phosphoramidate ligand **97** for the asymmetric isomerization of allylic alcohols (Scheme 2.4).[134]

[132] R. Hilgraf, A. Pfaltz, *Adv. Synth. Cat.* **2005**, *347*, 61.
[133] M. Schönleber, R. Hilgraf, A. Pfaltz, *Adv. Synth. Catal.* **2008**, *350*, 2033.
[134] J-Q. Li, B. Peters, P. G. Andersson, *Chem. Eur. J.* **2011**, *17*, 11143.



97

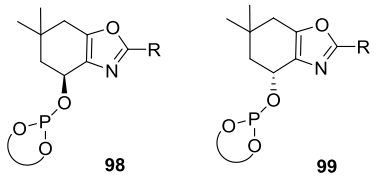


Scheme 2.4

The yields were moderate, however, the isomerization of both *E*- and *Z*-trisubstituted primary allylic alcohols to the corresponding chiral aldehydes was highly enantioselective.

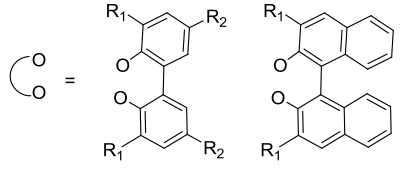
2.3.5 Oxazoline-Phosphite Ligands

A series of ligands easily accessible from hydroxyl–oxazole derivatives **98** and **99** was prepared in the group of Andersson and the complexes investigated in the Pd-catalyzed allylic substitution reaction of several substrates with different electronic and steric properties. By careful selection of the ligand components, high regio- and enantioselectivities (ee values up to 96%) and good activities were obtained in a broad range of mono-, di-, and trisubstituted linear hindered and unhindered substrates and cyclic substrates. NMR spectroscopic and DFT studies on the palladium-π-allyl intermediates provided a deeper understanding of the effect of ligand parameters on the origin of enantioselectivity.[135]



98

99



a R1 = R2 = *t*Bu
b R1 = *t*Bu, R2 = OMe
C R1 = $SiMe_3$, R2 = H

d (*S*) R1 = $SiMe_3$
e (*R*) R1 = $SiMe_3$
c (*S*) R1 = H
d (*R*) R1 = H

2.4 Supramolecular *P,N*-ligands – combinatorial approach

The supramolecular approach discussed in chapter 1 for the formation of SupraBox ligands has been extended to the formation of supramolecular phosphinooxazoline ligands.

[135] J. Mazuela, A. Paptchikhine, P. Tolstoy, O. Pàmies, M. Diéguez, P. G. Andersson, *Chem. Eur. J.* **2010**, *16*, 620.

It is based on the combination of two different monodentate ligands, respectively one P-ligand and one N-ligand, both bearing an urea moiety capable of hydrogen-bonding.

This approach, better known as combinatorial approach, foresees the simple mixing of ligands as an easy and fast way to generate a library of supramolecular bidentate ligands. The ease of this approach is an important feature because, despite significant progress in the field of theoretical and computational chemistry, there is still no rational way to model the best ligand for every given reactions and selectivity problems.

The combination of two different monodentate ligands was for the first time independently reported by Reetz and Feringa, de Vries in 2003 who developed numerous library of phosphonites, phosphites and phosphoramidites, forming complexes where two different ligands were coordinated to the same metal center and then they investigated their applications in various asymmetric transformations, mainly in hydrogenations.[136]

As already mentioned, the combinatorial approach relies on the addition of two ligands L_1 and L_2 to a metal source. In principle the two homocomplexes $[ML_1L_1]$ and $[ML_2L_2]$ and the heterocomplex $[ML_1L_2]$ can be formed, and the three of them could be in theory catalytically active. So, when the heterocomplex is the most selective species, the homocomplexes lower the overall selectivity of the process, unless the catalytic activity of the heterocomplex is exceedingly higher. However, in the worst case, is one of the homocomplexes, or even the two homocomplexes to be the most active species.

Under thermodynamic control (fast and reversible ligand exchange), the heterocomplex/ homocomplexes ratio often exceed the statistical value (2:1:1), and that the amount of heterocomplex can be enhanced by carefully tuning the L_1/L_2 ratio.[137,138]

More recently, the concept of supramolecular bidentate ligands emerged as a tool for the selective formation of heterocomplexes. This strategy requires that two ligands involved in the coordination process possess additional functionalities capable of interact each other shifting the equilibrium in the direction of the heterocomplex.[139]

The systems so created have less degrees of freedom, but still maintaining appeal for a combinatorial exploitation, compared to the analogs complexes with monodentate ligands.

---

[136] M. T. Reetz, A*ngew. Chem. Int. Ed.* **2008**, *47*, 2556.

[137] M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem. Int. Ed.* **2003**, *42*, 790; K. Ding, H. Du, Y. Yuan, J. Long, *Chem. Eur. J.* **2004**, *10*, 2872; A. Duursma, D. Peña, A. J. Minnaard, B. L. Feringa, *Tetrahedron Assym.* **2005**, 16, 1901; M. T. Reetz, X. Li, *Angew. Chem. Int. Ed.* **2005**, *44*, 2959; C. Monti, C. Gennari, U. Piarulli *Chem.-Eur. J.* **2007**, *13*, 1547.

[138] C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries, L. Lefort, *Chem. Eur. J.* **2005**, *11*, 6701.

[139] M. J. Wilkinson, P. W. N. M. van Leeuwen, J. N. H. Reek, *Org. Biomol. Chem*., **2005**, *3*, 2371; A. J. Sandee, J. N. H. Reek, *Dalton Trans*., **2006**, 3385; P. E. Goudriaan, P. W. N. M. van Leeuwen, M.-N. Birkholz, J. N. H. Reek, *Eur. J. Inorg. Chem*., **2008**, 2939; G. Gasparini, M. Dal Molin, L. J. Prins, *Eur. J. Org. Chem*., **2010**, 2429.

In fact they combine the most peculiar qualities of monodentate ligands (ease and speed of synthesis) with a conformational behavior similar to the classic bidentate ligands.

2.5 Development of a new class of supramolecular bidentate phosphinooxazoline ligands

We decided to extend the use the urea functionality as a *self*-complementary recognition motif for the formation of supramolecular bidentate ligands, for the synthesis of the first example of supramolecular phosphinoxazolines.

In analogy to the synthesis of SupraBox, the covalent linker was replaced by hydrogen-bond interactions between two urea moieties, connected to the oxazoline ring or to the phosphorus atom *via* different achiral spacers. Transition metal complexes of these phosphinoxazolines have been formed and preliminary attempts to apply them for asymmetric transformations have been done. In particular, Ir(I)-complexes have been applied in the hydrogenation of alkenes.

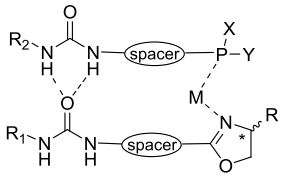


Figure 2.1

2.5.1 Synthesis of the urea-phosphine ligands

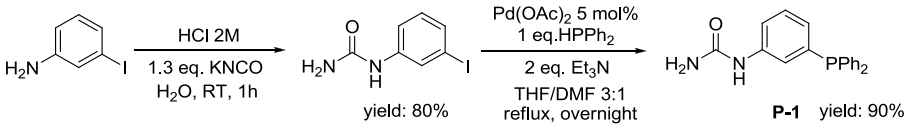
All the nitrogen-ligands (**Ox-3**, **Ox-4**, **Ox-6**, **Ox-8**, **Ox-12**, **Ox-13**, **Ox-15**, **Ox-16**) were synthesized as previously reported in chapter 1.

Also our phosphorous ligands were synthesized by a few step number synthesis, making them suitable for a combinatorial exploitation as well.

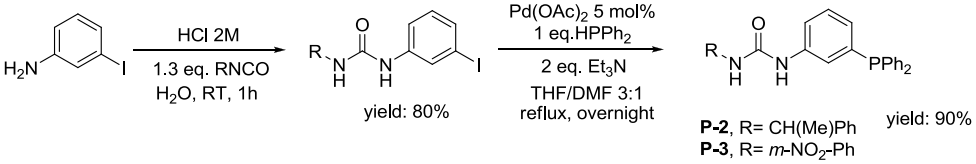
Likewise SupraBox ligands, the phosphorous ligands chosen possess in principle three possible tunable sites:

- the substitution at the phosphorous atom,
- the spacer,
- the urea substituents.

For ligands **P-1**, **P-2**, **P-3** the synthesis consisted in two straightforward synthetic steps (Scheme 2.5 for **P-1** and Scheme 2.6 for **P-2** and **P-3**).

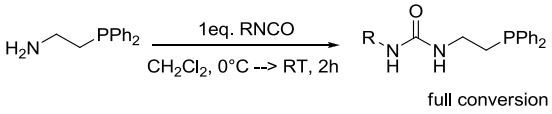


Scheme 2.5



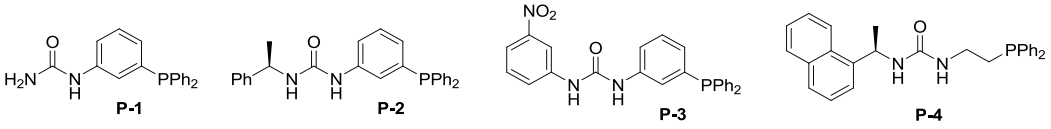
Scheme 2.6

The synthesis for **P-4** consisted only in the coupling between the aminophosphane and the chiral isocyanate (Scheme 2.7).



Scheme 2.7

A small library of 4 ligands, **P-1**, **P-2**, **P-3** and **P-4** was prepared and then the ligands were combined with SupraBox ligands in order to form iridium complexes.



2.5.2 Complexes formation and related complexation studies

First of all, studies to prove the formation of the desired complexes were needed.

As for SupraBox ligands, we exploited different techniques in order to verify and study the complexation.

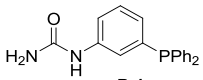
We focused the attention on Ir-complexes in order to finally use them in hydrogenation reactions of alkenes.

During the determination of the best way for their formation and use, some information already known concerning *P*,*N*-ligands Ir-complexes have been taken into account. In particular, we preserved the electrophilic nature of cationic iridium catalysts and avoided coordinating solvents and/or anions in order to prevent catalyst deactivation.

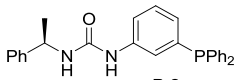
Dichloromethane and other chlorinated solvents are generally the most viable solvents for hydrogenation reactions, presumably since they all have high polarity but negligible coordinating power.[140] Indeed, when hydrogen-bond interactions occur, polar and protic solvents can interrupt the formation of these weak interactions. However, fluorinated alcohols, such as trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP), which are polar but with low hydrogen-bond acceptor properties, typically do not thwart and disturb the *self*-assembly of the catalyst. Thus they are sometimes used in the reactions, leading to better results than those with the use of dichloromethane as solvent.[141]

Concerning the couteranion, iridium complexes with bulky, apolar and extremely weakly coordinating anions, such as $BArF^-$ (Tetrakis[(3,5-trifluoromethyl)phenyl]borate), do not suffer from deactivation, due to the formation of hydride species, and are also less sensitive to moisture than the corresponding BF_4^- or PF_6^-.

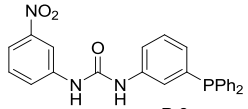
Few phosphorous-urea ligands **P-1 - P-4** were chosen. The spacer turned out to crucial for the formation of the heterocomplexes.



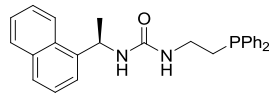
P-1



P-2



P-3



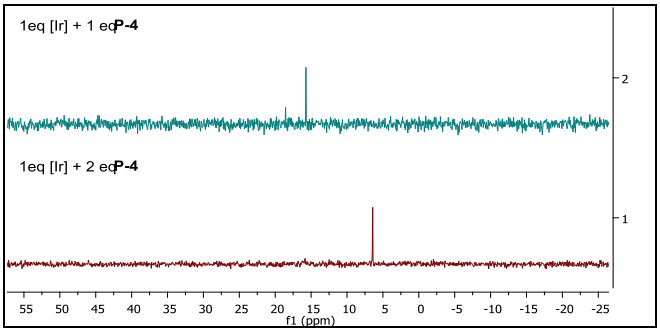
P-4

Indeed, phosphorus ligands possessing a rigid spacer (**P-1**, **P-2** and **P-3**) were deemed suitable for the combination with nitrogen ligands, whereas ligand **P-4**, with a flexible spacer, led to the exclusively formation of the complex arising from ligand **P-4** that behaved as a *P*,*O*-coordinating bidentate ligand,[142] while leaving the N-ligand not coordinated.

In Scheme 2.8 are reported the two ^{31}P-NMR spectra respectively relative to:

- the complex formed from 0.5 equiv. of $[Ir(cod)Cl]_2$ and 1 equiv. of ligand **P-4**.
- the complex formed from 0.5 equiv. of $[Ir(cod)Cl]_2$ and 2 equiv. of ligand **P-4**.

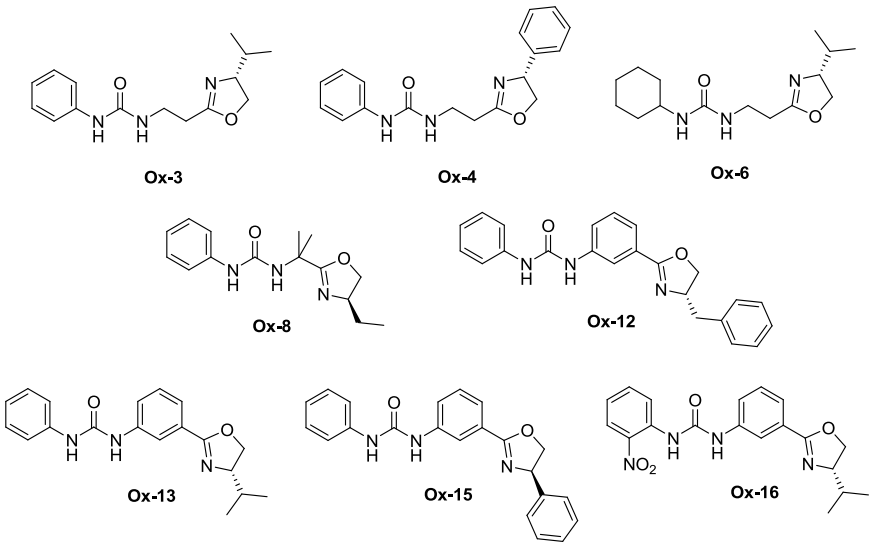
[140] C. Mazet, S. P. Smidt, M. Meuwly, A. Pfaltz, *J. Am. Chem. Soc*. **2004**, *126*, 14176.
[141] I. A. Shuklov, N. V. Dubrovina, E. Barsch, R. Ludwig, D. Michalika, A. Börner, *Chem. Commun*. **2009**, 1535.
[142] J. Meeuwissen, R. J. Detz, A. J. Sandee, B. de Bruin, J. N. H. Reek, *Dalton Trans.* **2010**, *39*, 1929.



Scheme 2.8

Considering that the peak of ligand **P-4** alone is at δ = -21.0 ppm, in the first case the complex is formed by ligand **P-4** that folds up and acts as *P*,*O*-coordinating bidentate ligand (δ = 15.7 ppm). While in the second case the complex consists in two molecules of P-ligand coordinated to the metal, therefore the second spectrum is relative to the Ir-homocomplex (δ = 6.4 ppm).

Concerning nitrogen ligands, some ligands from SupraBox library were chosen.



Among them, only those ligands with the linear aliphatic or the aromatic spacers fitted with the phosphorous ligands **P-1**, **P-2** and **P-3**. Indeed nitrogen ligand **Ox-8** never led to the formation of heterocomplexes.

In order to proceed with the complexation, $[Ir(cod)Cl]_2$ was chosen as iridium(I) source, once the preliminary attempts with Chlorobis(cyclooctene)iridium(I)dimer failed. Sodium(Tetrakis[(3,5-trifluoromethyl) phenyl]borate) (NaBArF) was chosen as couteranion exchanger, and then three phosphorous ligands and seven SupraBox ligands with different electronic and steric properties were chosen and combined to finally form seventeen heterocomplexes in total.

Different ligands ratio were tried, and the best conditions found for the complexation were Metal/P-ligand/N-ligand in dichloromethane in a 1:1:1 ratio. The three components were stirred at room temperature for 2 hours, then NaBArF was added and the resulting solution was stirred for an additional hour. Precipitated NaCl was removed by filtration.

The main problem concerning the complexation was the possible formation of a mixture of complexes (*i.e.* homocomplexes *vs* heterocomplex).

In general the equilibrium depends from different factors such as the intrinsic preference of the metal and the steric and electronic characteristics of the ligands.

In our case, the formation of a mixture of mono- and heterocomplexes occurred. These were investigated by ^{31}P-NMR as a very useful technique.

Ligands combination	P-homo-/heterocomplex ratio (from ^{31}P-NMR)	Conversion into the heterocomplex (from ^{31}P-NMR)
P-1/Ox-3	1/2	67%
P-1/Ox-4	1/3	75%
P-1/Ox-6	1/0.6	38%
P-1/Ox-12	1/38	43%
P-1/Ox-13	1/34	83%
P-1/Ox-15	0/1	100%
P-1/Ox-16	0/1	100%
P-2/Ox-3	1/1.5	60%
P-2/Ox-4	1/3	75%
P-2/Ox-6	1/0.2	17%
P-2/Ox-12	1/3.5	72%
P-2/Ox-13	1/4	80%
P-2/Ox-15	1/10	88%
P-2/Ox-16	0/1	100%

P-3/Ox-13	1/30	88%
P-3/Ox-15	1/3.5	63%
P-3/Ox-16	0/1	100%

Table 2.1

In the first column of Table 2.1 are reported the various combinations of phosphine and oxazoline ligands.

In the second column the ratio between the peak relative to the P-homocomplex and the peak of the heterocomplex. In few cases other peaks were present in the ^{31}P-NMR spectrum, but these were not further investigated. The third column is relative to the percentage of the heterocomplex in relation to the total of the species formed (identified by ^{31}P-NMR).

Here below are reported all the ^{31}P-NMR spectra.

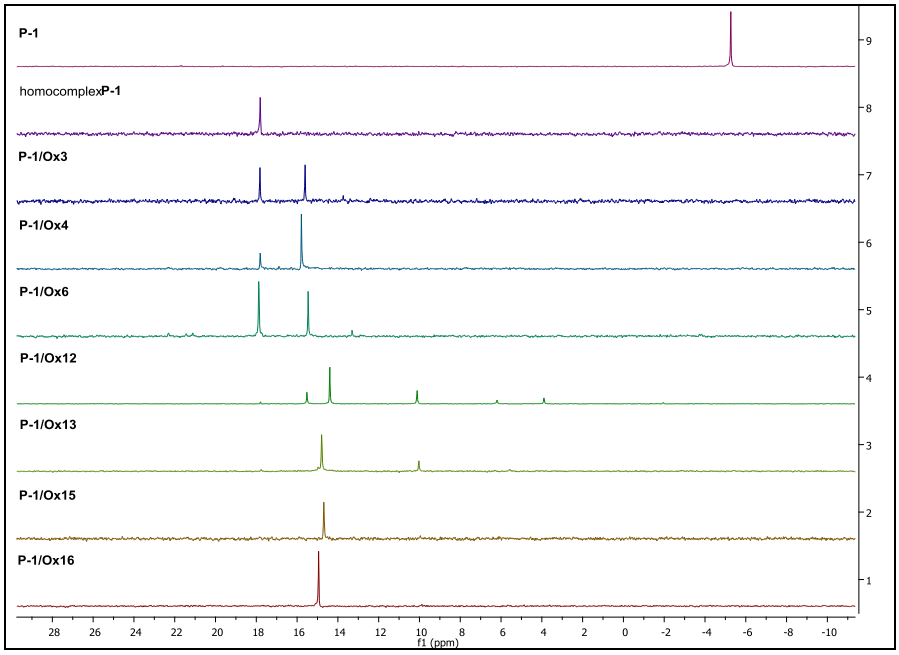


Figure 2.2

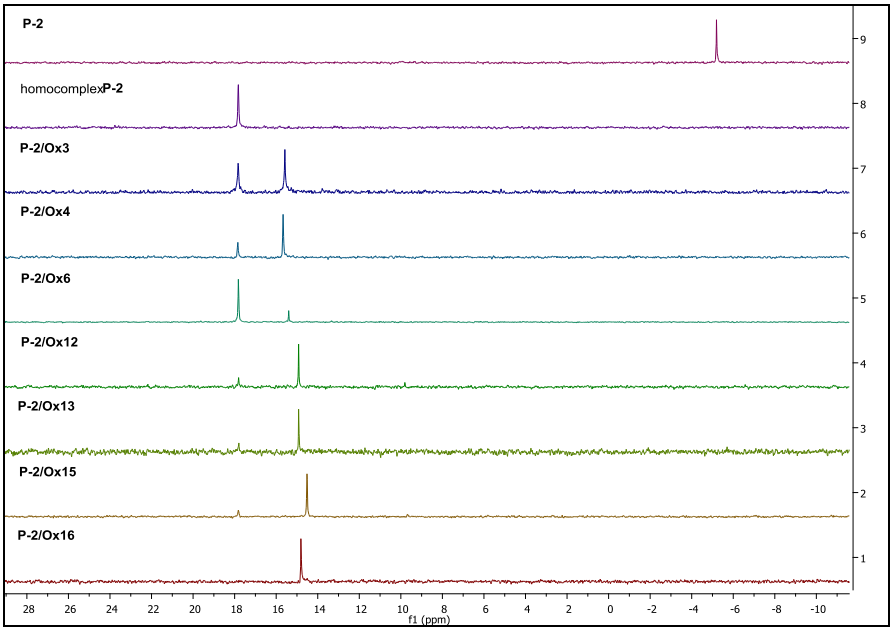


Figure 2.3

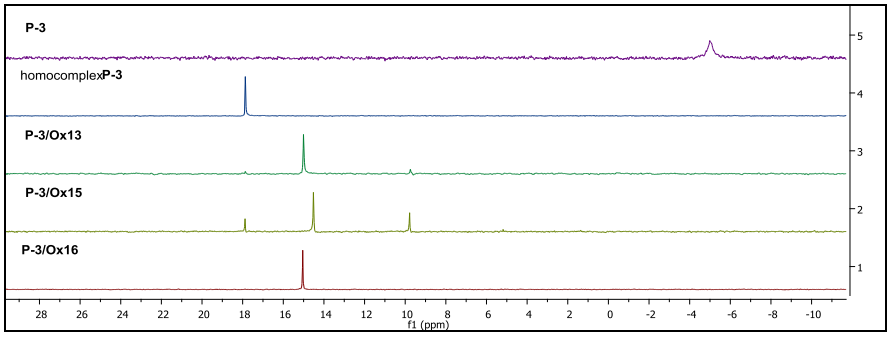


Figure 2.4

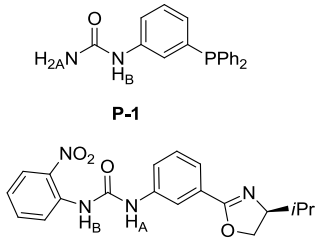
It is worth noting that, although the heterocomplexes were not always exclusively formed, these were the major species in the mixtures.

In addition, it is interesting to note that the combination with **Ox-16** as oxazoline ligand, always led to the selective formation of the heterocomplex, regardless of the UreaPhox. This behavior was most probably due to an additional interaction occurring between the nitro

group and the urea group of phosphorous ligands; although no deeper studies were done to confirm this hypothesis.

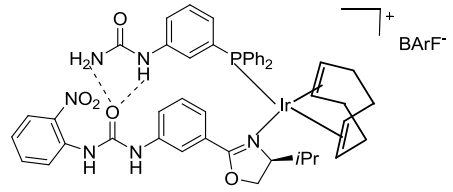
On the contrary, the same selection in the exclusively formation of the heterocomplexes was not observed when ligand **P-3**, possessing a nitro group in *meta* position, was combined with various nitrogen ligands. Most likely, in **P-3** the NO_2-group is too far away from the urea moiey of the nitrogen ligand to make this occurrence possible.

Pivotal for the investigation of the complexation were ^{1}H-NMR dilution studies, performed with ligand **P-1** and ligand **Ox-16**. The complexation studies were carried out using $[Ir(cod)Cl]_2$ as metal precursor, 1 equivalent of ligand **P-1** and 1 equivalent of ligand **Ox-16** in CD_2Cl_2 at room temperature. During these studies signals of the NHs of the free ligands were compared with those of the heterocomplex.



P-1

Ox-16

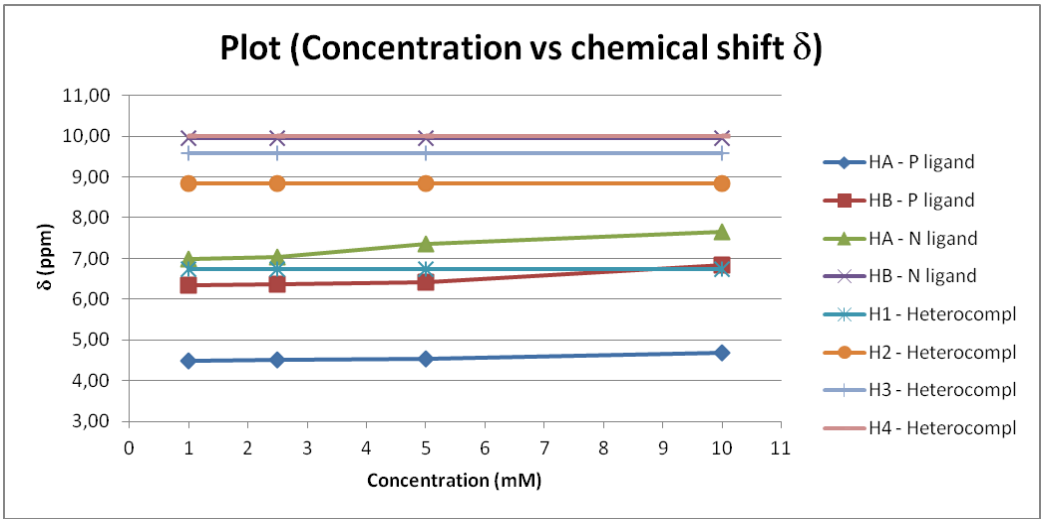


HETEROCOMPLEX

P-1	HA		HB	
concentration (mM)	δ1	Δδ1	δ2	Δδ2
1	4,50	**0,00**	6,35	**0,00**
2,5	4,52	**0,02**	6,38	**0,03**
5	4,54	**0,02**	6,42	**0,04**
10	4,68	**0,14**	6,83	**0,41**

(*S*) Ox-16	HA		HB	
concentration (mM)	δ1	Δδ1	δ2	Δδ2
1	6,99	**0,00**	9,96	**0,00**
2,5	7,04	**0,05**	9,96	**0,00**
5	7,36	**0,37**	9,96	**0,00**
10	7,65	**0,61**	9,96	**0,00**

Heterocomplex	H1		H2		H3		H4	
concentration (mM)	δ1	Δδ1	δ2	Δδ2	δ3	Δδ3	δ4	Δδ4
1	6,73	**0,00**	8,83	**0,00**	9,59	**0,00**	10,00	**0,00**
2,5	6,73	**0,00**	8,83	**0,00**	9,59	**0,00**	10,00	**0,00**
5	6,73	**0,00**	8,83	**0,00**	9,59	**0,00**	10,00	**0,00**
10	6,73	**0,00**	8,83	**0,00**	9,59	**0,00**	10,00	**0,00**



Dilution studies were performed by comparing signals of the urea protons by ^{1}H-NMR in a concentration range of 1-10 mM (1 - 2.5 - 5 - 10).

For both the nitrogen and phosphorus ligands, the urea proton signals showed dependency on concentration probably due to the formation of intermolecular hydrogen bonds,[143] except for H_B of **Ox-16**. The heterocomplex, on the other hand, shows four NH proton signals completely independent from the concentration. These results support the formation of the supramolecular bidentate species through urea hydrogen bonding.

Besides the ^{31}P-NMR spectroscopy, the HR-MS was certain a pivotal technique in order to define the occurred complexation and the heterocomplex formation. Hence, all the residues were analyzed by FAB-MS and the peaks relative to the heterocomplexes were detected in the spectra.

[143] A. Mulder, J. Huskens, D. N. Reinhoudt, *Org. Biomol. Chem.* **2004**, *2*, 3409.

2.5.3 Catalytic applications

2.5.3.1 Hydrogenation of alkenes

As we mentioned in the introduction, over the last decades, iridium complexes derived from chiral *P*,*N*-ligands have emerged as a new class of catalysts that has considerably enhanced the scope of asymmetric olefin hydrogenations.[144] Indeed, in contrast to rhodium and ruthenium phosphine catalysts, iridium catalysts do not require a polar coordinating group next to the C=C bond for high activity and enantioselectivity. In addition to unfunctionalized alkenes, high enantiomeric excesses were also obtained with various functionalized olefins for which no suitable chiral catalysts were available before.[145]

Our complexes were therefore tested in the hydrogenation of alkenes.

The heterocomplexes were prepared as previously mentioned, stirring 0.5 equivalent of $[Ir(cod)Cl]_2$, 1.0 equivalent of ligand **Ox** and 1.0 equivalent of ligand **P** in CH_2Cl_2 at room temperature for 2 hours. Then NaBArF was added and the resulting mixture were stirred for another hour. Finally NaCl was removed by filtration and the solvent evaporated.

All the residues were analyzed by ^{1}H-NMR, ^{31}P-NMR and mass spectrometry.

Not further purifications were done, since the good solubility of the complexes even in apolar solvents, caused by the introduction of $BArF^-$ as counteranion, made the crystallization difficult.

So, the supramolecular phosphinooxazoline iridium-complexes were subsequently used in hydrogenation reactions without further purification.

As shown in the section before, in some cases a mixture of homo- and heterocomplexes was formed. In these circumstances it is crucial to detect the activity of the homocomplexes; indeed, if the homocomplexes reveale to be unactive, we would be able to attribute the activity of the catalyst solely to the heterocomplexes.

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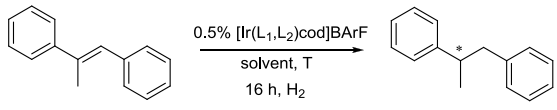
[144] J. Blankestein, A. Pfaltz, *Angew. Chem. Int. Ed.* **2001**, *40*, 4445; D.-R. Hou, J. Reibenspies, T. J. Calacot, K. Burgess, *Chem. Eur. J.* **2001**, *24*, 5391; G. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *334*, 4044; W-J. Lu, Y-W. Chen, X-L. Hou, *Angew. Chem. Int. Ed.* **2008**, *47*, 10133; S.-M. Lu, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 8920; A. Franzke, A. Pfaltz, *Chem. Eur. J.* **2011**, *17*, 4131.

[145] J. Blankestein, A. Pfaltz, *Angew. Chem. Int. Ed.* **2001**, *40*, 4445; A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wüstenberg, N. Zimmermann, *Adv. Synth. Catal.* **2003**, *345*, 33; S. McIntyre, E. Hörmann, F. Menges, S. P. Smidt, A. Pfaltz, *Adv. Synth. Catal.* **2005**, *347*, 282; M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem.* **2007**, *119*, 8422; *Angew. Chem. Int. Ed.* **2007**, *46*, 8274; M. Diéguez, J. Mazuela, O. Pàmies, J. J. Verendel, P. G. Andersson, *Chem. Commun.* **2008**, 3888; J. Mazuela, J. J. Verendel, M. Coll, B. Schäffner, A. Börner, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc.* **2009**, *131*, 12344.

Hydrogenation of alpha-methylstylbene

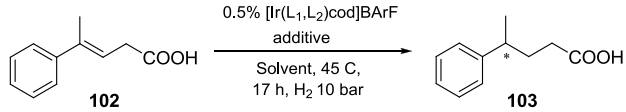


For this substrate, different condition were tested. In particular the reactions were initially carried out in dichloromethane at room temperature, both at 20 bar H_2 and 50 bar H_2. Firstly the homocomplexes were tested and no conversion was detected. Unfortunately also the use of the hetercomplexes led to the recovery of solely the unreacted alkene. The temperature was afterward increased at 45°C while the pressure of H_2 was holding at 50 bar. Beside the heterocomplexes were tested at the same condition but in trifluoroethane as solvent. Once again no hydrogenated substrate was recovered.

Since no conversion was obtained with unfuctionalized alkene **100**, we moved onto functionalized alkenes. The presence of a functional group in general helps the coordination of the substrate to the catalytically active metal center.

To test our complexes, both benchmark and challenging substrates were chosen.

Hydrogenation of *trans*-4-phenylpent-3-enoic acid



Entry	L_1, L_2	Additive (1 equiv.)	Solvent	Conversion[a] (%)
1	**P-1/Ox-13**	Et_3N	MeOH	-
2	**P-1/Ox-16**	Et_3N	MeOH	-
3	**P-1/Ox-13**		MeOH	7
4	**P-1/Ox-16**		MeOH	8
5	**P-1/Ox-13**	Et_3N	CH_2Cl_2	-
6	**P-1/Ox-16**	Et_3N	CH_2Cl_2	-
7	**P-1/Ox-13**		CH_2Cl_2	20
8	**P-1/Ox-16**		CH_2Cl_2	18
9	**P-1/Ox-13**	Et_3N	$(CF_3)_2CHOH$	-
10	**P-1/Ox-16**	Et_3N	$(CF_3)_2CHOH$	-
11	**P-1/Ox-4**		$(CF_3)_2CHOH$	100
12	**P-1/Ox-13**		$(CF_3)_2CHOH$	98

13	**P-1/Ox-16**		$(CF_3)_2CHOH$	100
14	**P-2/Ox-13**		$(CF_3)_2CHOH$	100
15	**P-2/Ox-16**		$(CF_3)_2CHOH$	100

[a] Calculated on the methylesther from ^{1}H-NMR spectrum after work up with a solution of trimethysylyldiazomethano 2M and then CH_3COOH

Table 2.2

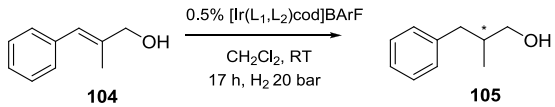
Reactions in MeOH as solvent did not proceed. This fact confirms that standard protic solvents are not suitable for supramolecular species (entries 3 and 4) hampering H-bond interactions. Quite interestingly the use of dichloromethane was not successful and only moderate conversions were achieved.

The addition of TEA as additive, which in other examples reported in the literature used in order to deprotect the carboxylic acid functionality helping the coordination to the metal center,[146] in our case did not improve the reactivity. This might be due to the presence of 1 equivalent of triethylammonium chloride which hampers the formation of the supramolecular bidentate complex.

Very satisfactory results in terms of conversion were achieved when $(CF_3)_2CHOH$ was the solvent used (entries 11 to 15), although racemic products were in all cases invariably obtained.

The lack in enantioselectivity was attributed to the flexibility of the heterocomplexes, compared to the classical covalent *P*,*N*-ligands, typically creating a 5- or 6-terms iridacycle when coordinated to the metal.

Hydrogenation of *trans*-2-methyl-3-phenylprop-2-en-1-ol



104 **105**

Entry	L_1, L_2	Conversion[a] (%)
1	**$(P\text{-}1)_2$**	100%
2	**$(P\text{-}2)_2$**	60%
3	**P-1/Ox-3**	10%
4	**P-1/Ox-4**	10%
5	**P-1/Ox-13**	10%
6	**P-1/Ox-15**	5%

[146] Q.-L. Zhou, *Angew. Chem. Int. Ed.*, **2012**, 51, 2708.

7	**P-1/Ox-16**	10%
8	**P-2/Ox-3**	5%
9	**P-2/Ox-4**	5%
10	**P-2/Ox-13**	5%
11	**P-2/Ox-15**	5%
12	**P-2/Ox-16**	10%

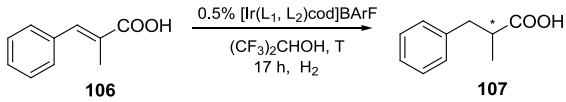
[a] Calculated on the methylesther from ^{1}H-NMR spectrum after work up with a solution of trimethysylyldiazomethano 2M and then CH_3COOH

Table 2.3

In these reactions the two phosphorus homocomplexes **P-1** and **P-2** initially tested, proved to be more active than the heterocomplexes. Therefore, the low values of conversion observed with the heterocomplex catalysts obtained in mixture with the homocomplexes (entries 3, 4, 8, 9) could in principle be attributed to the activity of the homocomplexes.

However, no further investigations were done since was not achieved enantiodiscrimination.

Hydrogenation of alpha-methylcinnamic acid



Entry	L_1, L_2	additive (1eq)	Temperature	H_2 pressure	Conversion[a] (%)
1	**P-1/Ox-4**		RT	10 bar	12
2	**P-1/Ox-4**	Et_3N	RT	10 bar	-
3	**P-2/Ox-4**		RT	10 bar	45
4	**P-2/Ox-4**	Et_3N	RT	10 bar	-
5	**P-1/Ox-3**		45° C	10 bar	50
6	**P-1/Ox-4**		45° C	10 bar	15
7	**P-1/Ox-13**		45° C	10 bar	16
8	**P-1/Ox-15**		45° C	10 bar	10
9	**P-1/Ox-16**		45° C	10 bar	75
10	**P-2/Ox-3**		45° C	10 bar	60
11	**P-2/Ox-4**		45° C	10 bar	55
12	**P-2/Ox-13**		45° C	10 bar	50
13	**P-2/Ox-15**		45° C	10 bar	30
14	**P-2/Ox-16**		45° C	10 bar	33
15	**$(P-1)_2$**		45° C	10 bar	100

16	**$(P\text{-}2)_2$**		45° C	10 bar	70
17	**$(Ox\text{-}4)_2$**		45° C	10 bar	80

[a] Calculated on the methylesther from ^{1}H-NMR spectrum after work up with a solution of trimethysylyldiazomethano 2M and then CH_3COOH

Table 2.4

Regarding the hydrogenation of substrate **106**, first of all two complexes [Ir(**P-1**/**Ox-4**)(cod)]BArF and [Ir(**P-2**/**Ox-4**)(cod)]BArF where tested in $(CF_3)_2CHOH$ at room temperature both with (entries 2 and 4) and without 1 equivalent of Et_3N (entries 1 and 3) as additive. Once again the use of Et_3N gave not conversion.

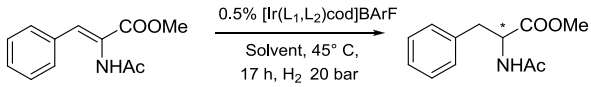
To increase the final conversion, the reactions were tried at 45°C (entries 6 and 11). At this temperature the reactions showed the best results in terms of yield. So other complexes were investigated (entries 5, 7, 8, 9, 10, 12, 13, 14).

Some homocomplexes were tested as well (entries 15 to 17), and these trials revealed that, for this substrate, the homocomplexes behaved as the most active species.

Consequently, the lower conversions with the use of the two heterocomplexes is either due to the lower activity of the pure heterocomplex or, at worst, to the completely inactivity of it.

The lack in enantioselectivity did not prompt us into further investigations.

Hydrogenation of 2-acetylamino-3-phenyl-acrylic acid methyl ester



108 **109**

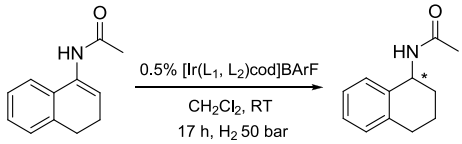
Entry	L_1, L_2	Solvent	Conversion[a] (%)
1	**P-1/Ox-4**	CH_2Cl_2	70
2	**P-1/Ox-16**	CH_2Cl_2	80
3	**P-2/Ox-4**	CH_2Cl_2	85
4	**P-1/Ox-4**	$(CF_3)_2CHOH$	98
5	**P-1/Ox-16**	$(CF_3)_2CHOH$	100
6	**P-2/Ox-4**	$(CF_3)_2CHOH$	100

[a] Determined by GC, column Supelco β-dex 225

Table 2.5

Even for this substrate, $(CF_3)_2CHOH$ proved to increase the conversion (entries 4 to 6) but, once again, these heterocomplexes shown to be not able to induce enantiodiscrimination.

Hydrogenation of *N*-(3,4-dihydronaphthalen-1-yl)acetamide



110 **111**

Entry	L_1, L_2	Conversion[a] (%)
1	**P-1/Ox-4**	25
2	**P-1/Ox-13**	31
3	**P-1/Ox-15**	22
4	**P-2/Ox-16**	41
5	**P-3/Ox-16**	33
6	**$(P\text{-}1)_2$**	14
7	**$(P\text{-}2)_2$**	14
8	**$(P\text{-}3)_2$**	19
9	**$(Ox\text{-}4)_2$**	33
10	**$(Ox\text{-}13)_2$**	9
11	**$(Ox\text{-}15)_2$**	32
12	**$(Ox\text{-}16)_2$**	18

[a] Determined by GC, column Supelco β-dex 225

Table 2.6

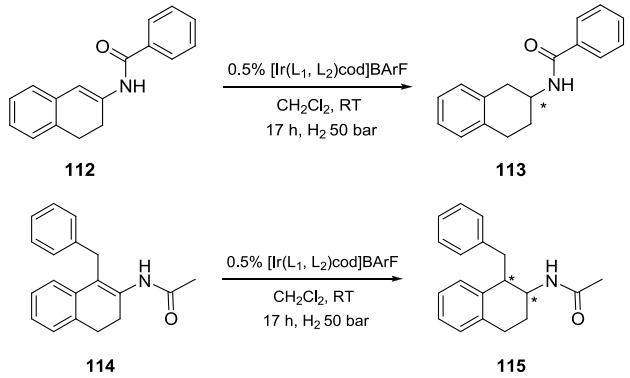
Several heterocomplexes were tested for the hydrogenation of substrate **110**, as well as the relative homocomplexes. The employment of the heterocomplexes as catalysts did not improve the results.

Once again the conversion into the final product **111** was achieved, revealing that the species were active as catalysts but not a discrimination in terms of enantioselectivity was obtained.

Hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)benzamide and *N*-(1-benzyl-3,4-dihydronaphthalen-2-yl)acetamide

So far our complexes revealed to be in general active for the conversion of the chosen olefins, but the lack in enantioselectivity was attributed to the flexibility of our supramolecular bidentate ligands compared with the rigid structure of the classical covalent bidentate *P*,*N*-ligand.

Therefore, we wanted to see if our complexes could be suitable for the hydrogenation of hindered C=C double bonds. The two substrates **112** and **114** following reported were thus chosen and tested.



Various heterocomplexes were used as catalysts as well as the relative homocomplexes.
The reactions were carried out at room temperature with H_2 pressure of 50 bar, but unfortunately, the conversion of these bulky substrates was very low. Hence, the two substrates revealed to be challenging also for our complexes.

2.6 Conclusions

Novel supramolecular bidentate *P*,*N*-ligands were synthesized, in particular phosphinooxazoline ligands raised from the hydrogen bond-induced assembly of one phosphine ligand and one oxazoline ligand, both bearing an urea functionality.
Different techniques confirmed the formation of the heterocomplexes, although in some cases in mixture with the relative homocomplexes.
The iridium-complexes resulted often inactive species for hydrogenation reactions of unfunctionalized alkenes. Unfortunately not satisfying results in terms of enantioselectivity were obtained, probably due to the flexible structure of the supramolecular bidentate ligands.
However, the predominant, and in some cases exclusive, formation of the heterocomplexes achieved with this type of supramolecular interaction, will lead us to further future investigations of the complexes in other applications, in particular in allylic alkylations.

2.7 Experimental section

General Remarks

All reactions were carried out under a nitrogen atmosphere, using standard Schlenk techniques.

The reactions were performed with distilled solvents. CH_2Cl_2 and MeOH were distilled from CaH_2 and TFE and HFIP over molecular sieves under nitrogen.

Air sensitive liquids and solutions were transferred via a gas-tight syringe or cannula.

Removal of solvents was accomplished by evaporation on a Buchi rotary evaporator (water bath 40°C) or directly from the Schlenk using an oil pump.

The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness). Visualisation was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution or a nynhidrine solution. Flash column chromatography was performed using silica gel (60 Å, particle size 40-64 μm) as stationary phase, following the procedure by Still and co-workers.[147] ^{1}H-, ^{13}C- and ^{31}P-NMR spectra were recorded measured on a Bruker DRX 400MHz and Inova 500MHz.

Chemical shifts are reported in ppm with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded with a 400 MHz spectrometer operating at 100.56 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.23 ppm). ^{31}P NMR spectra were referenced to external H_3PO_4. Chiral GC separations were conducted on Interscience HR-GC apparatus with a Supelco β-dex 225 column. High resolution mass spectra were recorded on a JEOL JMS SX/S102A four sector mass spectrometer, equipped with ESI or FAB source. Chiral HPLC analysis were performed with a Shimadzu instrument equipped with a Diode Array detector.

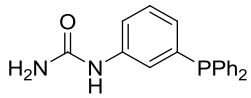
Commercially available reagents were used as received without, unless indicated otherwise.

[147] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

2.7.1 Synthesis and characterization of the ligands

Ligands **Ox-3**, **Ox-4**, **Ox-6**, **Ox-8**, **Ox-12**, **Ox-13**, **Ox-15**, **Ox-16** were synthesized according to Chapter 1 (Experimental section).

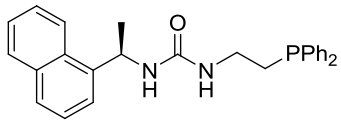
1-(3-(diphenylphosphino)phenyl)urea (**P-1**)



Compound **P-1** was synthesized according to a published procedure.[148]

Crude yield (^{31}P NMR): 96 % - **^{1}H NMR** (400 MHz, CD_2Cl_2): δ = 4.56 (s, 2H), 6.36 (s, 1H), 7.02-7.09 (m, 2H), 7.29-7.36 (m, 10H), 7.45-7.46 (m, 1H). - **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = -4.09. Spectroscopic data of the product were in agreement with the literature.

(R)-1-(2-(diphenylphosphino)ethyl)-3-(1-(naphthalen-1-yl)ethyl)urea (**P-2**)

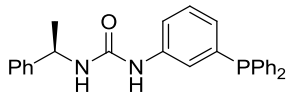


Compound **P-4** was synthesized according to a published procedure.[149]

Crude yield (^{31}P NMR): 90 % - **^{1}H NMR** (400 MHz, CD_2Cl_2): δ = 1.4 (d, 3H, *J* = 6.6 Hz), 2.1 (m, 2H), 3.1 (m, 2H), 5.15 (m, 1H), 5.42 (d, 1H*J* = 7.5 Hz), 5.5 (t, 1H, *J* = 6.6 Hz). - **^{31}P NMR** (121.2 MHz, CD_2Cl_2):

δ = -21.00. Spectroscopic data of the product were in agreement with the literature.

(*R*)-1-(3-(diphenylphosphino)phenyl)-3-(1-phenylethyl)urea (**P-2**)



In a 500 mL flask, meta-iodoaniline (5.48g, 25 mmol) was dissolved in 12.5 mL of HCl in H_2O (2M). 100mL of water was added to dissolve completely the solid. (*R*)-(+)-α-Methylbenzyl isocyanate (4.7mL, 33 mmol) was dissolved in a minimum volume of water and was added dropwise to the solution. After 1h stirring at r.t. a white precipitate was filtered

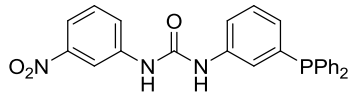
[148] P-A. R. Breuil, F. W. Patureau, J. N. H. Reek, *Angew. Chem. Int. Ed.* **2009**, *48*, 2162.
[149] J. Meeuwissen, M. Kuil, A. M. van der Burg, A. J. Sandee, J. N. H. Reek, *Chem. Eur. J.* **2009**, *15*, 10272.

and washed with water. The product was then washed twice with toluene, and dried under vacuum to afford the (*R*)-1-(3-iodophenyl)-3-(1-phenylethyl)urea (yield: 80%).

(*R*)-1-(3-iodophenyl)-3-(1-phenylethyl)urea (2.92g, 8 mmol) was dissolved in 20 mL of a solution of THF/DMF (3/1), NEt_3 (2.20mL, 16 mmol) and Ph_2PH (1.39mL, 8 mmol) were successively added. $Pd(OAc)_2$ (90mg, 5 mol%) was added under Argon. The black solution was refluxed overnight. After cooling to room temperature, the THF was evaporated (crude yield ^{31}P NMR 90 %). 20 mL of degassed water was added. The product was extracted with ethyl acetate. The solvent was evaporated. The crude mixture was dissolved in DCM and filtrated over a plug of SiO_2. The plug was washed with DCM until the impurities had passed, and then was pushed through with ethyl acetate. After evaporation of the solvent the product was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO): δ = 1.34 (d, 3H, *J*= 8 Hz), 4.76 (dq, 1H, *J*=8.0, 16.0 Hz), 6.56 (d, 1H, *J*= 8 Hz), 6.73 (t, 1H, *J*=8.0Hz), 7.17-7.43 (m, 17H),7.47 (d, 1H, *J*= 12 Hz), 8.43 (s, 1H) - **^{13}C NMR** (100.6 MHz, CD_2Cl_2): δ = 21.4, 56.9, 121.8, 125.9, 126.7, 126.9, 128.5, 128.6, 128.9, 129.5, 129.7, 133.9, 136.7, 138.4, 139.0, 141.5, 154.3 - **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = -5.19 **- HR-MS**: $[M+H]^+$ *m/z*: 425.17.

1-(3-(diphenylphosphino)phenyl)-3-(3-nitrophenyl)urea (**P-3**)



In a 500 mL flask, meta-iodoaniline (5.48g, 25 mmol) was dissolved in 12.5 mL of HCl in H_2O (2M). 100mL of water was added to dissolve completely the solid. 3-nitro-phenylisocyanate (5.4g, 33 mmol) was dissolved in a minimum volume of water and was added dropwise to the solution. After 1h stirring at r.t. a yellow precipitate was filtered and washed with water. The product was then washed twice with toluene, and dried under vacuum to afford the 1-(3-iodophenyl)-3-(3-nitrophenyl)urea (yield: 82%).

1-(3-iodophenyl)-3-(3-nitrophenyl)urea (3 g, 8 mmol) was dissolved in 20 mL of a solution of THF/DMF (3/1), NEt_3 (2.10mL, 15 mmol) and Ph_2PH (1.39mL, 8 mmol) were successively added. $Pd(OAc)_2$ (90mg, 0.5 mol%) was added under Argon. The black solution was refluxed overnight. After cooling to room temperature, the THF was evaporated (crude yield ^{31}P NMR 92 %). 20 mL of degassed water was added. The product was extracted with ethyl acetate. The solvent was evaporated. The crude mixture was dissolved in DCM and filtrated over a plug of SiO_2. The plug was washed with DCM until the impurities had passed, and then was

pushed through with ethyl acetate. After evaporation of the solvent the product was obtained as a yellow solid.

^{1}H NMR (400 MHz, DMSO): δ = 7.44 (t, 1H, *J*= 8 Hz), 7.84-7.89 (m, 4H), 7.91-7.95 (m, 2H), 8.00-8.04 (m, 5H), 8.12-8.20 (m, 3H), 8.27 (d, 1H, *J*=8.0Hz), 8.41 (dd, 1H, *J*= 4, 8 Hz), 9.09 (t, 1H, *J*= 2 Hz), 9.52 (s, 1H), 9.76 (s, 1H) - **^{13}C NMR** (100.6 MHz, CD_2Cl_2): δ = 114.5, 119.4, 121.8, 125.9, 127.8, 128.6, 128.9, 129.5, 129.7, 129.9, 133.9, 136.7, 136.8, 138.4, 139.0, 148.5, 153.9 - **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = -5.04 - **HR-MS**: $[M+H]^+$ *m/z*: 442.13.

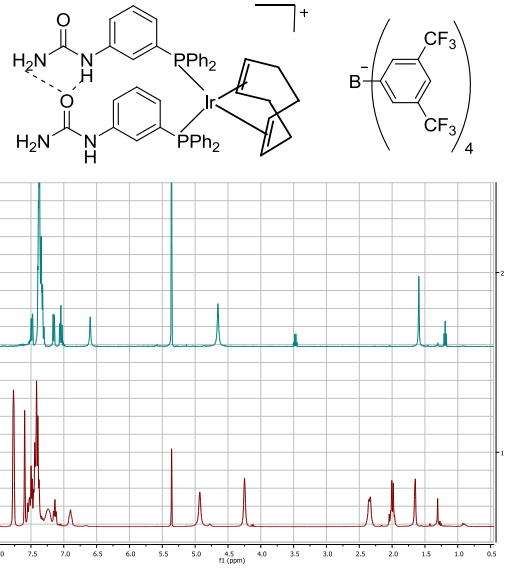
2.7.2 Synthesis and characterization of metal complexes

2.7.2.1 General procedure for the formation of the homocomplexes

In a dry Schlenk, $[Ir(cod)Cl]_2$ (0.5 equiv.) and the ligand (2 equiv.) were dissolved in CH_2Cl_2 and the solution stirred at room temperature for 2 hours. Sodium(Tetrakis[(3,5-trifluoromethyl) phenyl]borate) was added, leaving the mixture stirring for another hour. The mixture was filtered under nitrogen over celite and then the solvent evaporated under vacuum. The residue were characterized by ^{1}H-, ^{31}P-NMR, FAB-MS.

For each complexes, the comparison between the ^{1}H-NMR spectrum of the ligand itself and the ^{1}H-NMR spectrum of the corresponding Ir-homocomplex is reported.

$[Ir(P\text{-}1)_2(cod)]BArF$

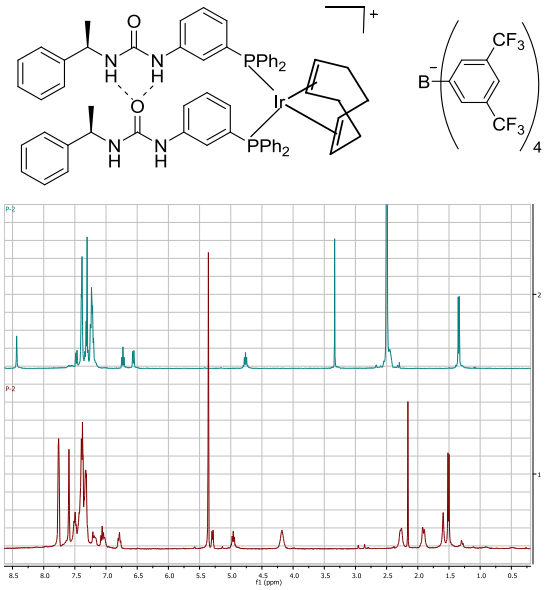


^{1}H-NMR: comparison between the ligand and homocomplex spectra

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 1.90-2.11 (m, 4H), 2.32-2.40 (m, 4H), 4.25 (bs, 4H), 4.93 (bs, 4H), 6.90 (bs, 2H), 7.13 (t, 2H, *J*=7.6 Hz), 7.23-7.32 (m, 4H), 7.39-7.55 (m, 24H), 7.60 (s, 4H), 7.77 (s, 8H).

Red powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 17.9. – **HR-MS**: $[M]^+$ *m/z*: 942.30

[Ir(P-2)$_2$(cod)]BArF

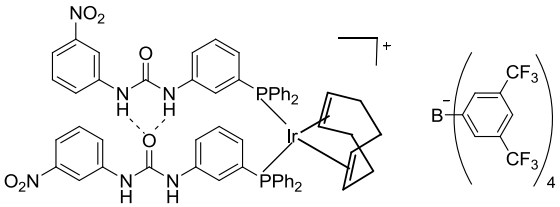


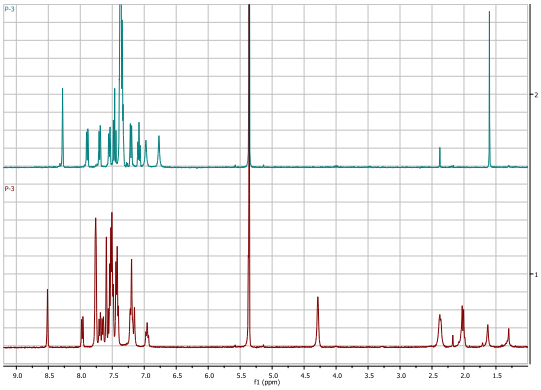
^{1}H-NMR: comparison between the ligand and homocomplex spectra

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 1.51 (d, 6H, *J*=6.9 Hz), 1.86-1.93 (m, 4H), 2.23-2.34 (m, 4H), 4.18 (bs, 4H), 4.92-4.99 (m, 2H), 4.29 (d, 2H, *J*=7.4 Hz), 6.78 (t, 2H, *J*=8.2 Hz), 7.01-7.08 (m, 4H), 7.14-7.21 (m, 4H), 7.30-7.51 (m, 26H), 7.60 (s, 4H), 7.77 (s, 8H).

Red powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 17.8 – **HR-MS**: $[M]^+$ *m/z*: 1149.83

[Ir(P-3)$_2$(cod)]BArF



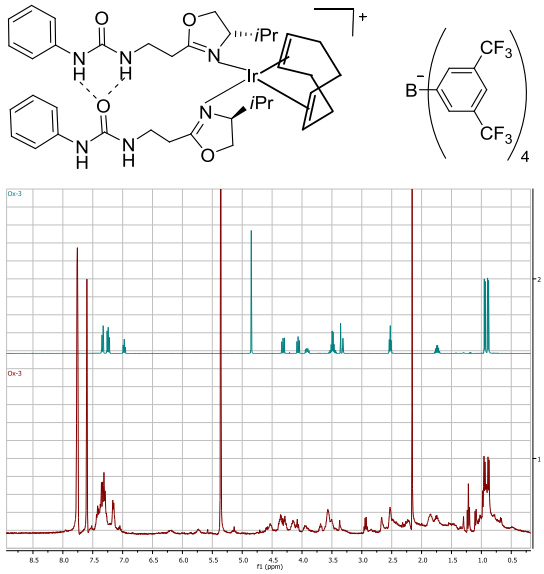


^{1}H-NMR: comparison between the ligand and homocomplex spectra

^{1}H-NMR (400 MHz, DMSO): δ = 1.99-2.08 (m, 4H), 2.35-2.42 (m, 4H), 4.28 (bs, 4H), 6.95 (t, 2H, *J*=8.0 Hz), 7.14-7.23 (m, 8H), 7.39-7.44 (m, 8H), 7.48-7.56 (m, 10H), 7.59 (s, 4H), 7.64 (d, 2H, *J*=7.7 Hz), 6.69 (d, 2H, *J*=7.7 Hz), 7.77 (s, 8H), 7.97 (d, 2H, *J*=8.0 Hz), 8.51-8.54 (m, 2H).

Red powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 17.9. - **HR-MS**: $[M]^+$ *m/z*: 1183.31

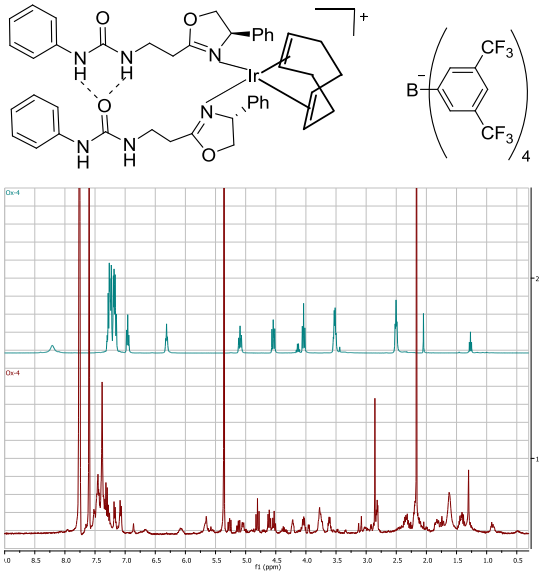
[Ir(Ox-3)$_2$(cod)]BArF



^{1}H-NMR: comparison between the ligand and homocomplex spectra

Yellow powder, **HR-MS**: $[M]^+$ *m/z*: 851.44

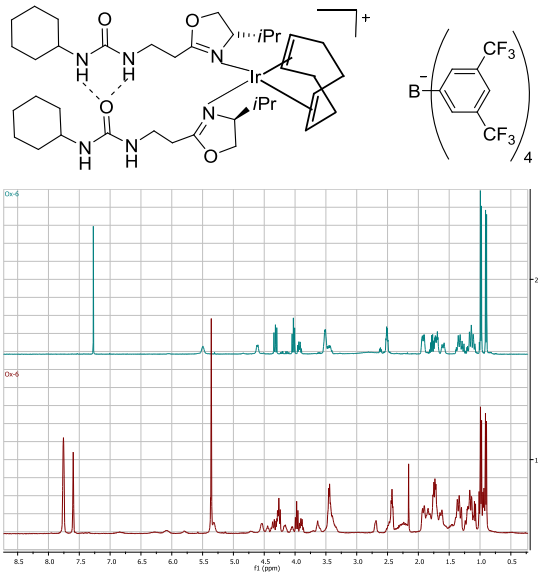
[Ir(Ox-4)$_2$(cod)]BArF



^{1}H-NMR: comparison between the ligand and homocomplex spectra

Yellow powder, **HR-MS**: $[M]^+$ *m/z*: 919.45

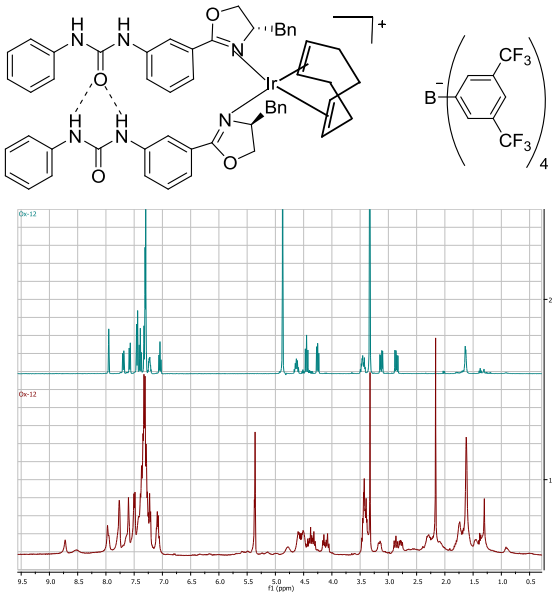
[Ir(Ox-6)$_2$(cod)]BArF



^{1}H-NMR: comparison between the ligand and homocomplex spectra

Yellow powder, **HR-MS**: $[M]^+$ *m/z*: 865.39

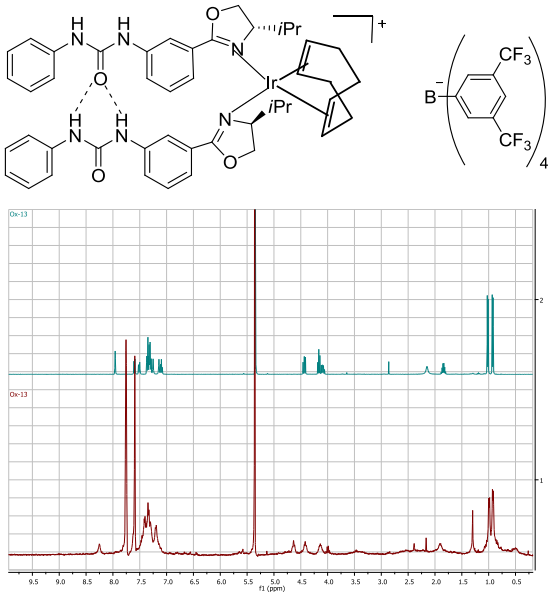
[Ir(Ox-12)$_2$(cod)]BArF



^{1}H-NMR: comparison between the ligand and homocomplex spectra

Yellow powder, **HR-MS**: $[M]^+$ *m/z*: 1043.44

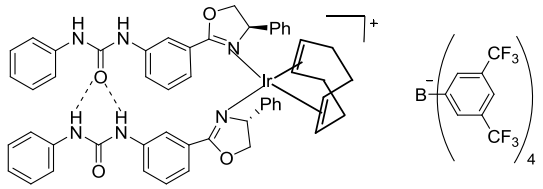
[Ir(Ox-13)$_2$(cod)]BArF

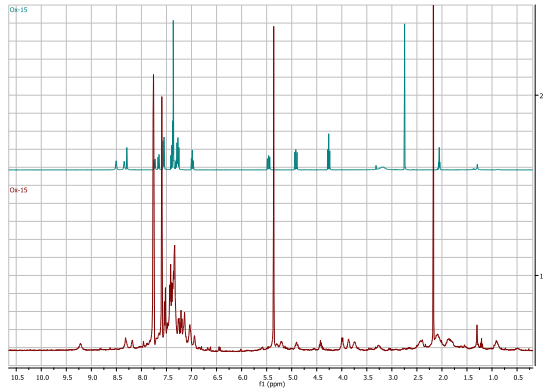


^{1}H-NMR: comparison between the ligand and homocomplex spectra

Yellow powder, **HR-MS**: $[M]^+$ *m/z*: 945.42

[Ir(Ox-15)$_2$(cod)]BArF

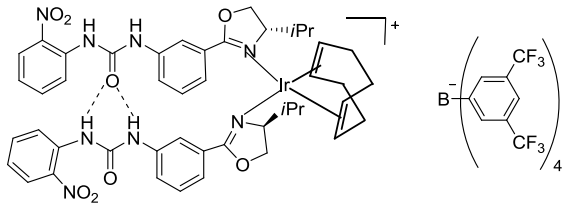


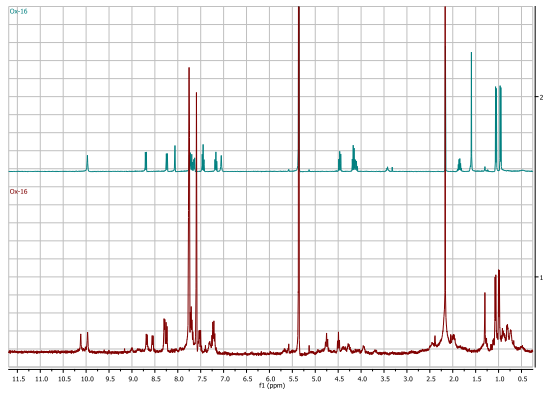


^{1}H-NMR: comparison between the ligand and homocomplex spectra

Yellow powder, **HR-MS**: $[M]^+$ *m/z*: 1015.39

[Ir(Ox-16)$_2$(cod)]BArF





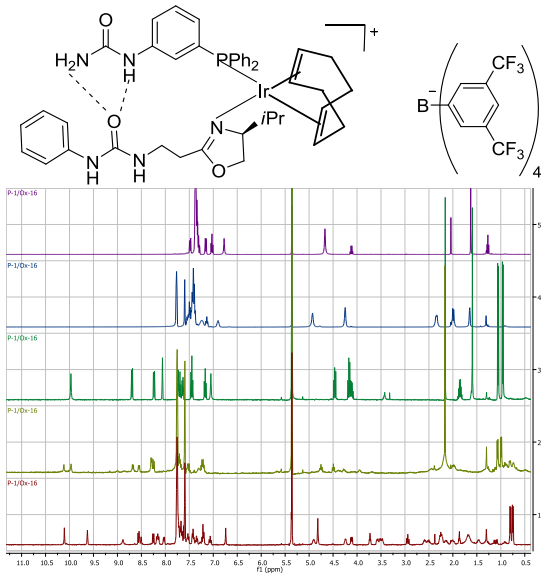
^{1}H-NMR: comparison between the ligand and homocomplex spectra

Yellow powder, **HR-MS**: $[M]^+$ *m/z*: 1037.39

2.7.2.2 General procedure for the formation of the heterocomplexes

In a dry Schlenk, $[Ir(cod)Cl]_2$ (0.5 equiv.) and the N-ligand (1 equiv.) and the P-ligand (1 equiv.) were dissolved in CH_2Cl_2 and the solution stirred at room temperature for 2 hours. Sodium(Tetrakis[(3,5-trifluoromethyl) phenyl]borate) was added, leaving the mixture stirring for another hour. The mixture was filtered over celite under nitrogen and then the solvent evaporated under vacuum. The residue were characterized by ^{1}H-, ^{31}P-NMR, FAB-MS.
For each complexes, the comparison between the ^{1}H-NMR spectra of the P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex is reported.

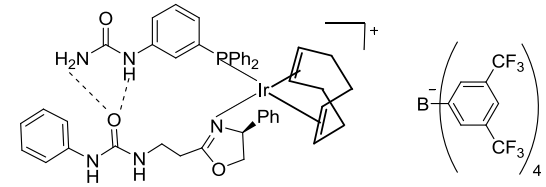
[Ir(P-1)(Ox-3)(cod)]BArF

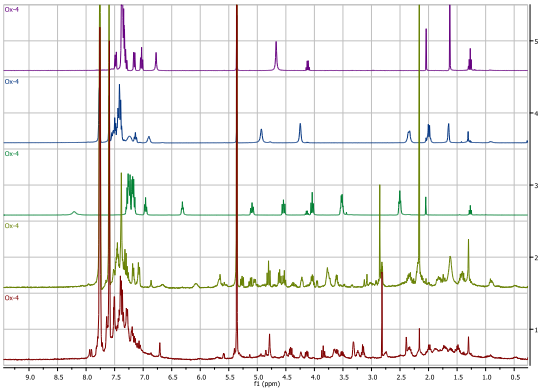


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.6. – **HR-MS**: $[M]^+$ *m/z*: 896.36

[Ir(P-1)(Ox-4)(cod)]BArF

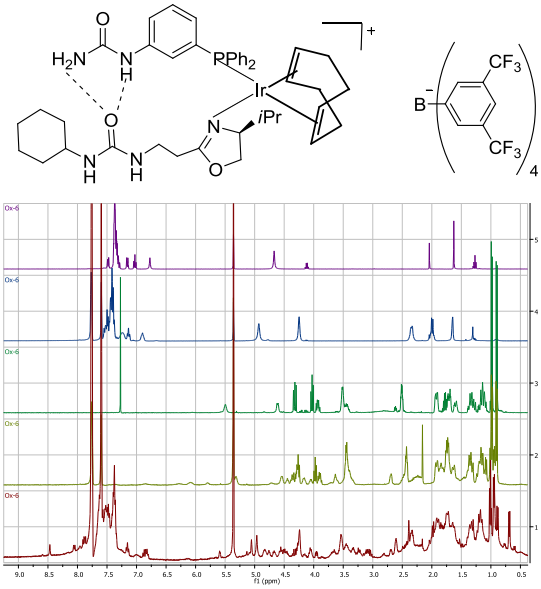




^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.8, **HR-MS**: $[M]^+$ *m/z*: 930.34

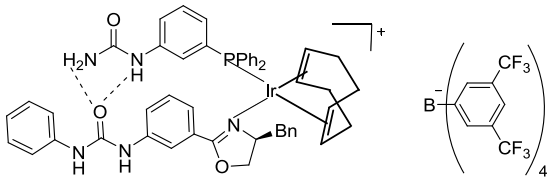
[Ir(P-1)(Ox-6)(cod)]BArF

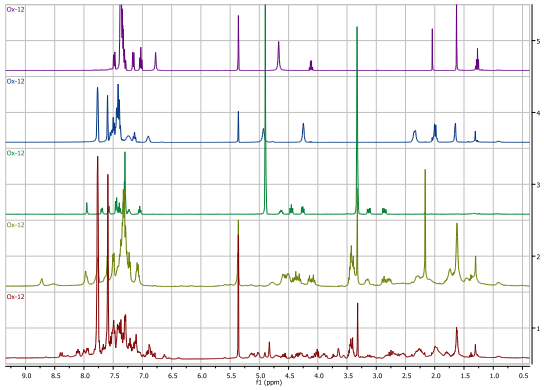


^{1}H-NMR: comparison of the spectra relative to the: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.4, **HR-MS**: $[M]^+$ *m/z*: 906.41

[Ir(P-1)(Ox-12)(cod)]BArF

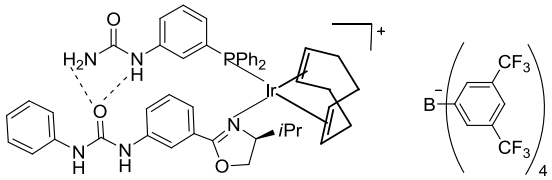


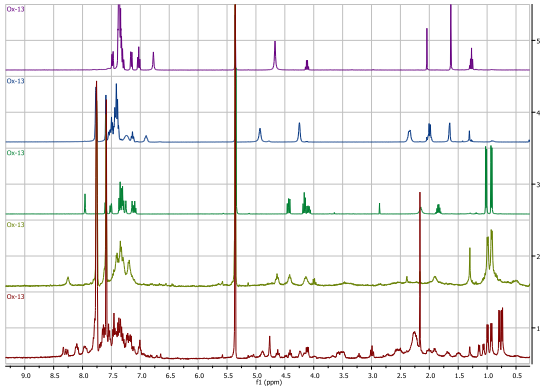


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 14.4, **HR-MS**: $[M]^+$ *m/z*: 993.36

[Ir(P-1)(Ox-13)(cod)]BArF

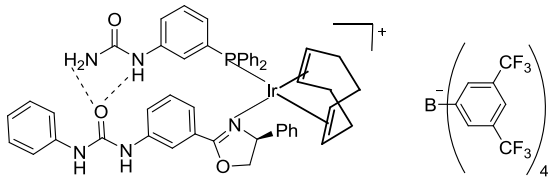


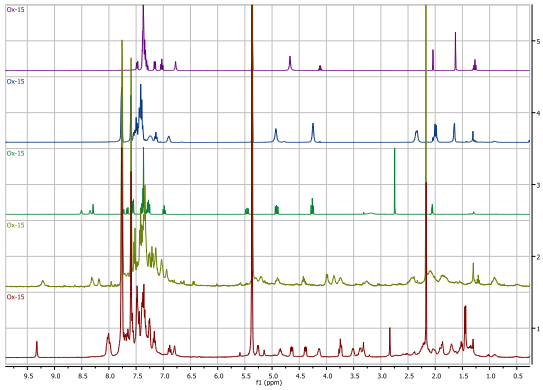


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 14.8, **HR-MS**: $[M]^+$ *m/z*: 944.36

[Ir(P-1)(Ox-15)(cod)]BArF

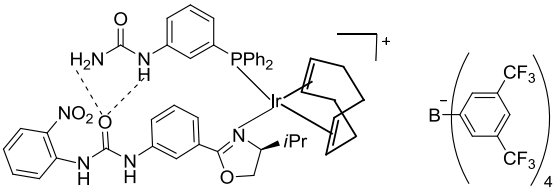


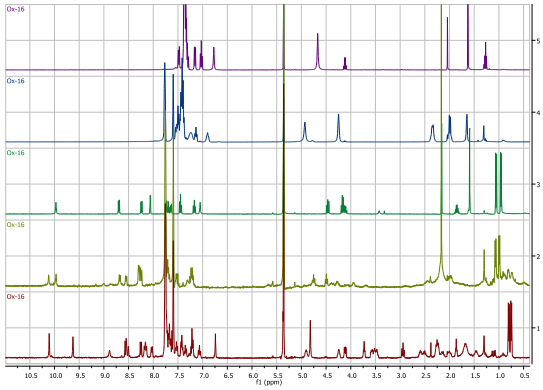


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 14.7, **HR-MS**: $[M]^+$ *m/z*: 978.34

[Ir(P-1)(Ox-16)(cod)]BArF

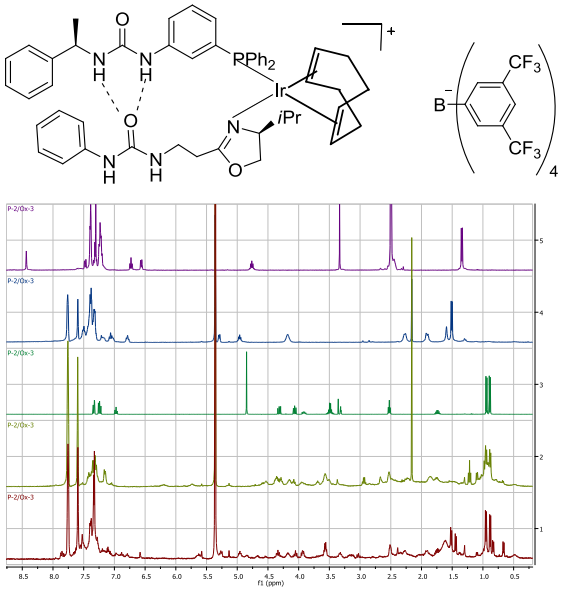




^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.0, **HR-MS**: $[M]^+$ *m/z*: 989.34

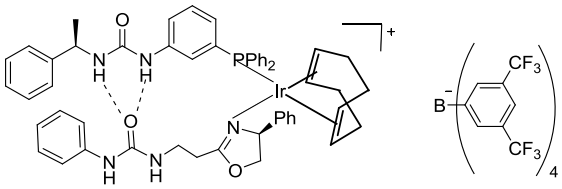
[Ir(P-2)(Ox-3)(cod)]BArF

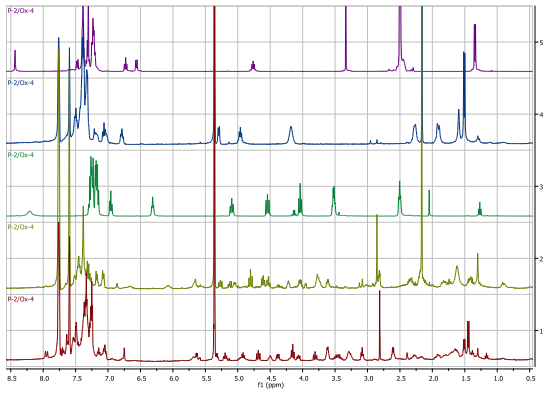


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.6, **HR-MS**: $[M]^+$ *m/z*: 1001.36

[Ir(P-2)(Ox-4)(cod)]BArF

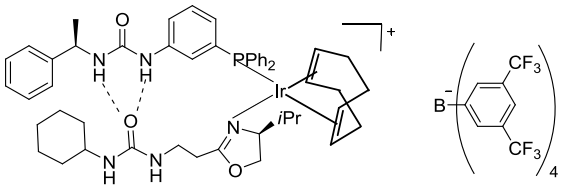


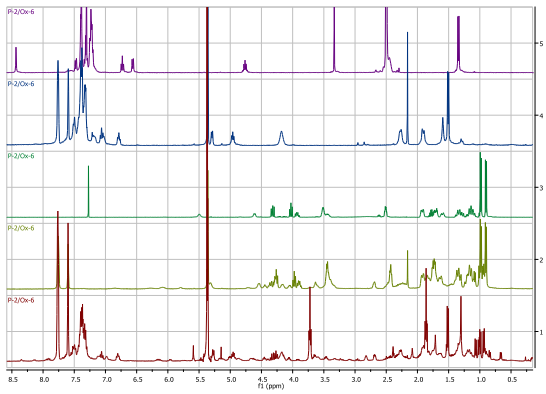


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.7, **HR-MS**: $[M]^+$ *m/z*: 134.36

[Ir(P-2)(Ox-6)(cod)]BArF

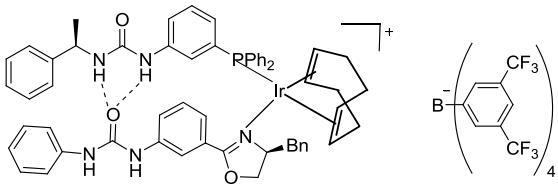


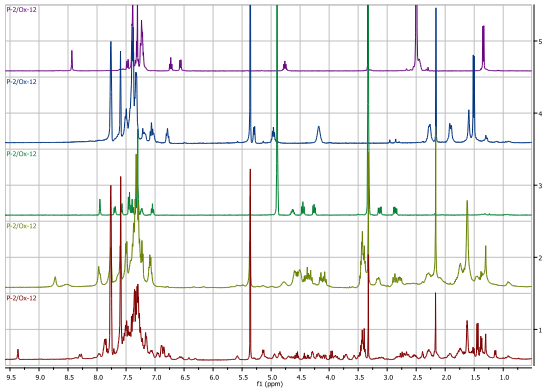


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.4, **HR-MS**: $[M]^+$ *m/z*: 1010.47

[Ir(P-2)(Ox-12)(cod)]BArF

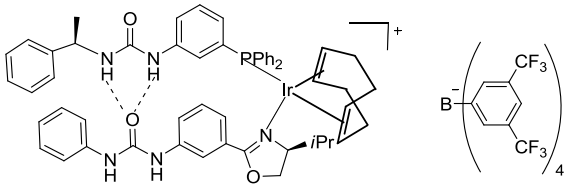


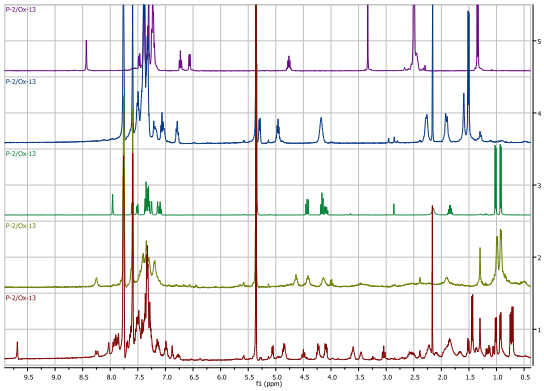


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.0, **HR-MS**: $[M]^+$ *m/z*: 1097.37

[Ir(P-2)(Ox-13)(cod)]BArF

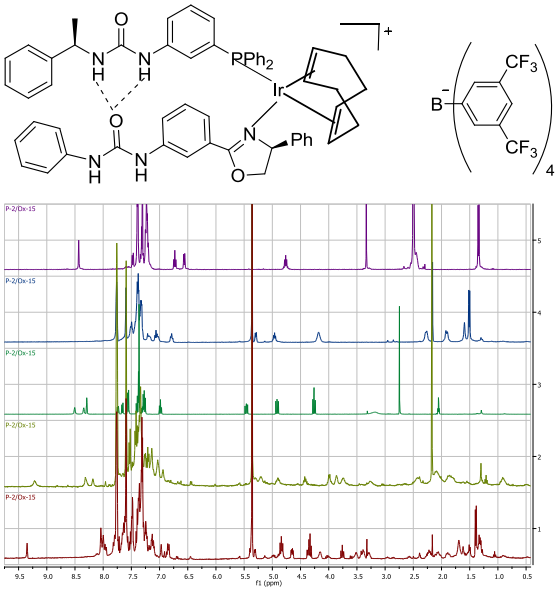




^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.0, **HR-MS**: $[M]^+$ *m/z*: 1048.32

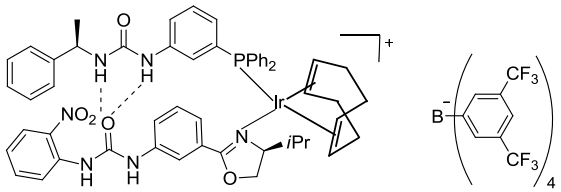
[Ir(P-2)(Ox-15)(cod)]BArF

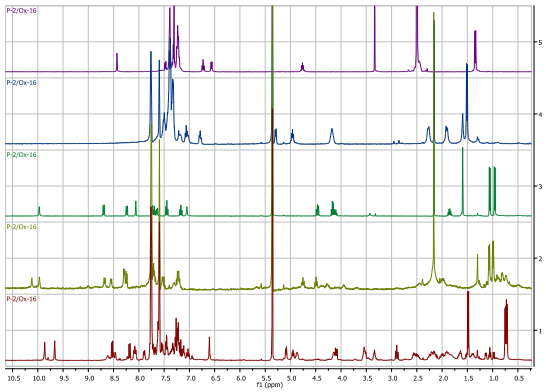


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 14.5, **HR-MS**: $[M]^+$ *m/z*: 1082.34

[Ir(P-2)(Ox-16)(cod)]BArF

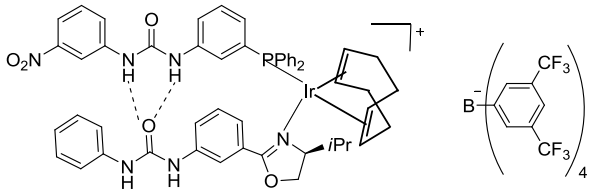


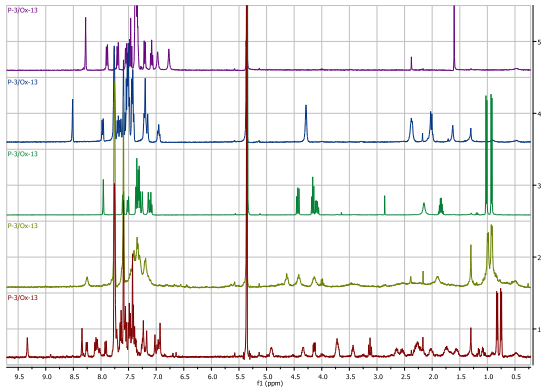


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 14.8, **HR-MS**: $[M]^+$ *m/z*: 1093.32

[Ir(P-3)(Ox-13)(cod)]BArF

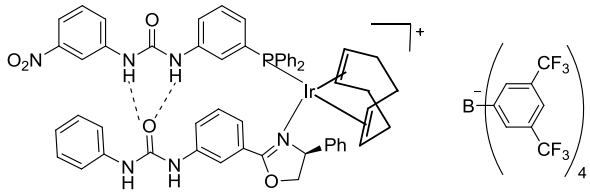


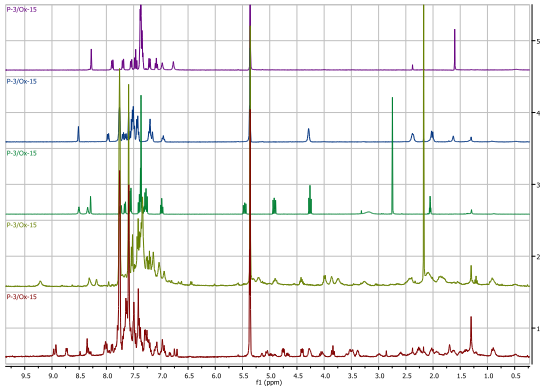


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.0, **HR-MS**: $[M]^+$ *m/z*: 1065.32

[Ir(P-3)(Ox-15)(cod)]BArF

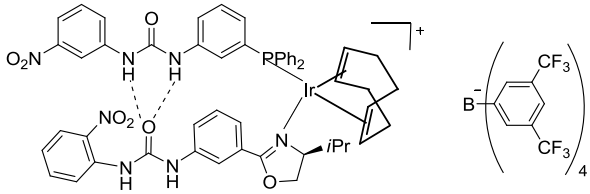


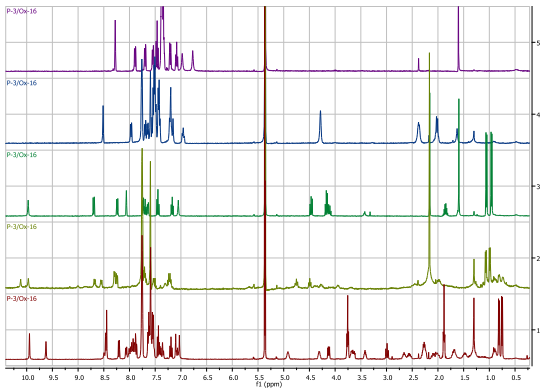


^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 14.5, **HR-MS**: $[M]^+$ *m/z*: 1099.36

[Ir(P-3)(Ox-16)(cod)]BArF





^{1}H-NMR: comparison of the spectra relative to: P-ligand, P-ligand homocomplex, N-ligand, N-ligand homocomplex and the heterocomplex

Orange powder, **^{31}P NMR** (121.2 MHz, CD_2Cl_2): δ = 15.1, **HR-MS**: $[M]^+$ *m/z*: 1110.36

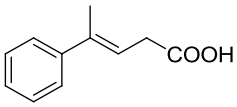
Dilution studies - NMR evaluations

The ^{1}H NMR dilution experiments were carried out by preparing a sample (0.7 mL) at a known concentration: 1, 2.5, 5, 10 mM in CD_2Cl_2 for **Ox-16**, **P-1**, and **[Ir(P-1/Ox-16)(cod)]BArF**. The position of the solvent signal was used as a reference for the urea NH signal.

2.7.3 Hydrogenation reactions

Substrates **100**, **106** and **108** are commercially available.

trans-4-phenylpent-3-enoic acid (**102**)

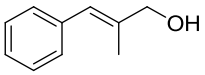


Compound **102** was synthesized according to a published procedure.[150]

^{1}H NMR (400 MHz, CD_3Cl): δ = 2.07 (s, 3H),3.31 (d, 2H, *J* = 7.1 Hz), 5.93 (t, 1H, *J* = 7.0 Hz), 7.24–7.26 (m, 1H), 7.32 (t, 2H, *J* = 7.5 Hz), 7.40 (d, 2H, *J* = 7.7 Hz). Spectroscopic data of the product were in agreement with the literature.

[150] S. Song, S-F. Zhu, S. Yang, S. Li, Q-L. Zhou, Angew. Chem. Int. Ed. **2012**, *51*, 2708.

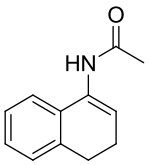
trans-2-methyl-3-phenylprop-2-en-1-ol (**104**)



Compound **104** was synthesized according to a published procedure.[151]

^{1}H NMR (400 MHz, CD_3Cl): δ = 1.90 (s, 3H), 4.18 (s, 2H), 6.53 (s, 1H), 7.20-7.35 (m, 5H). Spectroscopic data of the product were in agreement with the literature.

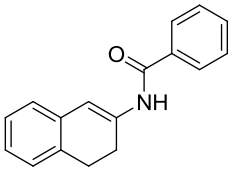
N-(3,4-dihydronaphthalen-1-yl)acetamide (**110**)



Compound **110** was synthesized according to a published procedure.[152]

^{1}H NMR (400 MHz, CD_3Cl): δ = 2.14 (s, 3H), 5.09 (s, 1H), 5.88 (s, 1H), 6.84 (s, 1H), 7.33-7.55 (m, 5H). Spectroscopic data of the product were in agreement with the literature.

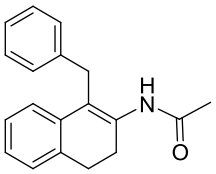
N-(3,4-dihydronaphthalen-2-yl)benzamide (**112**)



Compound **112** was synthesized according to a published procedure.[153]

^{1}H NMR (400 MHz, CD_3Cl): δ = 2.55 (t, 2 H, *J* = 7.7 Hz), 2.93 (t, 2 H, *J* = 7.7 Hz), 7.07-7.80 (m, 11 H). Spectroscopic data of the product were in agreement with the literature.

N-(1-benzyl-3,4-dihydronaphthalen-2-yl)acetamide (**114**)



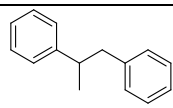
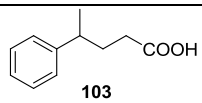
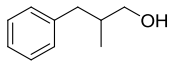
Compound **114** was synthesized according to a published procedure.[154]

[151] L. Cheng-Kun, L. Ta-Jung, *J. Org. Chem.* **2008**, *73*, 9527.
[152] D. J. Frank, A. Franzke, A. Pfaltz, Chem. – Eur. J. **2013**, *19*, 2405.
[153] G. Argouarch, O. Samuel, H. B. Kagan, *Eur. J. Org. Chem.* **2000**, 2885.

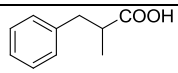
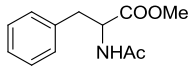
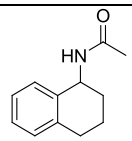
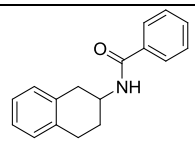
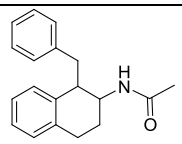
^{1}H NMR (400 MHz, CD_3Cl): δ = 1.90 (s, 3H), 2.62 (t, 2 H, *J* = 7.7 Hz), 2.93 (t, 2 H, *J* = 7.7 Hz), 3.22 (s, 2H) 7.07-7.80 (m, 10 H). Spectroscopic data of the product were in agreement with the literature.

- General procedure for the hydrogenation reactions

The hydrogenation experiments were carried out in a stainless steel autoclave (150 mL) charged with an insert suitable for 14 reaction vessels (including Teflon mini stirring bars) for conducting parallel reactions. In a typical experiment, the reaction vessels were charged with substrate, Ir-complex and Et_3N, if needed, in dry solvent (so that the concentration of the substrate was 0.25 M). Before starting the catalytic reactions, the charged autoclave was purged three times with H_2, then filled to the required pressure with H_2. The reaction was stirred at room temperature or 45°C for the time needed before the H_2 pressure was released. For some substrate pretreatments were required before the analysis, for some others no pretreatments were needed and the solvent was just removed in vacuum. Conversions were determined by ^{1}H NMR spectroscopy and ee% values were determined using chiral GC or HPLC.

ENTRY	PRODUCT Spectral data match those previously reported.	PRETRATMENT	SEPARATION METHOD
1	 **101** *Adv. Synth. Cat.* **2013**, *355*, 880.		HPLC. Column OJ-H, Heptane/IPA 99:1, flow 0.7 mL/min
2	 **103** *Angew. Chem. Int. Ed*. **2012,** *51*, 2708.	Conversion into the methylesther by work up with a solution of trimethysylyldiazomethano 2M and then CH_3COOH	HPLC. Column OJ-H, Heptane/IPA 95:5, flow 0.7 mL/min
3	 **105** *Tetrahedron*, **2011**, 67, 5421.	Conversion into the methylesther by work up with a solution of trimethysylyldiazomethano 2M and then CH_3COOH	HPLC. Column Chiracel OD-H, Heptane/IPA 95:5, flow 0.5 mL/min

[154] P. Dupau, C. Bruneau, P. H. Dixneuf, *Adv. Synth. Cat.* **2001**, *343*, 331.

4	 **107** *Angew. Chem. Int. Ed*. **2012**, *51*, 8872.	Conversion into the methylesther by work up with a solution of trimethysylyldiazomethano 2M and then CH_3COOH	HPLC. Column Chiracel OD-H, Heptane/IPA 95:5, flow 1.0 mL/min
5	 **109** *Org. lett*., **2000,** *2*, 2431.		GC (column Supelco β-dex 225) Conditions: 140 °C for 14 min, then gradient: 50°C/min to 220 °C; t_S= 11.56 min, t_R = 12.14 min; $t_{substrate}$ = 10.77 min.
6	 **111** *Org. lett*., **2007,** *9*, 1157.		GC (column Supelco β-dex 225) Conditions: 70°C for 1 min, then gradient: 10°C/min to 160 °C, then 160° for 5.0 min, then gradient: 4°C/min to 220 C; t_R = 27.78 min, t_S = 27.92 min, $t_{substrate}$= 32.63 min.
7	 **113** *Eur. J. Org. Chem*, **2000**, 16, 2885.		HPLC. Column Chiracel AD, Heptane/IPA 90:10, flow 0.6 mL/min
8	 **115** *Adv. Synth. Cat.*,**2001**, 343, 331.		HPLC. Column Chiracel AD, Heptane/IPA 90:10, flow 0.6mL/min

Chapter 3

Synthesis of polydentate nitrogen ligands for iron-complexes

3.1 Introduction on iron-based catalysis

As we have pointed out so far, transition metal catalysis has a tremendous importance in the field of modern synthesis; indeed many processes only take place when metal complexes offer new reaction pathways. Nevertheless, the number of industrially implemented catalytic processes is still rather limited, and this is even more pronounced in asymmetric catalysis. In spite of all advances in the technology, most of the enantiopure compounds are obtained via classical resolution of diastereomeric salts. The main reason for this paradox is the high cost of the catalysts, classically noble metals such as Rh, Ru, Ir, Pd, Pt, of limited supply.

It is therefore quite obvious that replacing precious metals with cheap first-row transition metals would turn out in a great breakthrough, from both the scientific and the industrial point of view.[155] Among the possible suitable metals, iron plays a special role. In contrast to toxic metals (i.e. Cr, Os, Co..), iron is a physiologically and environmentally friendly metal. The large abundance of iron in earth's crust (4.5 wt%, it is the fourth most abundant element and the second most common metal in the Earth's crust, after aluminium) makes it very cheap and offers the possibility to engage iron even in stoichiometric manner.

Despite these obvious advantages, only few iron complexes are nowadays used for synthetic applications. Among them, iron carbonyl complexes[156] and ferrocene derivatives[157] are the most prominent examples.

At the moment, chemists aim at developing iron-based catalysts not only for hydrogenation but also for a variety of organic transformations that can be used in future industrial applications.

To this end, one major obstacle in replacing precious metals with iron stems from the difference in electronic structure. Whereas a noble metal like platinum easily undergoes two-electron redox changes to promote bond-making and breaking events, iron is more prone to one-electron redox changes. This tendency, which poses challenges for controlling reactivity and stabilising or maintaining the function of the catalyst, can be circumvented by the use of "non-innocent" ligands. By confining all redox changes to the ligand, no oxidation state change would occur at the metal, thus avoiding the formation of true Fe(0) species, which are

[155] *Iron Catalysis in Organic Chemistry: Reactions and Applications*, Wiley-VCH, **2008**; R. H. Morris, *Chem. Soc. Rev.* **2009**, *38*, 2282; R. M. Bullock, *Catalysis without Precious Metals*, Wiley-VCH, **2010**.
[156] R. Langer, G. Leitus, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2011**, *50*, 2120; A. Berkessel, S. Reichau, A. von der Höh, N. Leconte, Jörg-M. Neudörlf, *Organometallics*, **2011**, *30*, 3880.
[157] S. Fleischer, S. Zhou, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 5120.

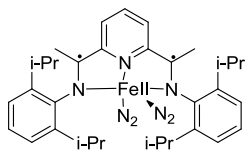
sometimes detrimental in reduction catalysis, because they can decompose by ligand loss and result in deposition of the metal.[158]

Here below some applications of iron-complexes in catalysis will be highlighted.

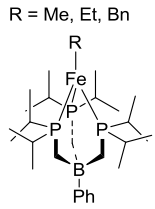
3.2. Iron-catalyzed reduction of C-C multiple bonds (alkenes and alkynes)

Compared to the other transition metals (Pd, Pt, Rh, Ir), iron is significantly less exploited for the homogeneous catalysis of organic reactions in general, and of double bond reductions in particular. However, given its far lower cost and greater abundance over the more precious metals, in recent years there has been a growing scientific effort for developing efficient and selective homogeneous iron-catalysts.[155] Given the indispensability of alkene and alkyne hydrogenation in fine and commodity chemical synthesis,[159] these transformations are important targets for the more environmentally benign catalytic methods.

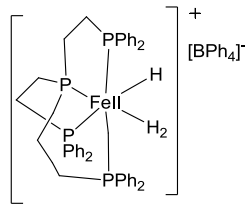
Complexes **116**, **117**, **118** are examples of iron catalysts studied by Chirik, Peters and Bianchini in the reduction of C-C multiple bonds. Complexes **116** and **117** are extremely air-sensitive; their synthesis and manipulation must take place under rigorously dry conditions and these serious practical limitations have prevented their industrial application; whereas complex **118** is reported as exhibiting exceptional thermal and chemical stability.



116



117



118

In particular, complex **116**, used by Chirik,[160] was suitable for the hydrogenation of several types of olefins under very mild conditions, and showed a broad functional group tolerance (unsaturated ethers, esters, hydrocarbons, amines). The first mechanism proposed was based on a Fe(0)/Fe(II) cycle, but later a combination of spectroscopic techniques and density

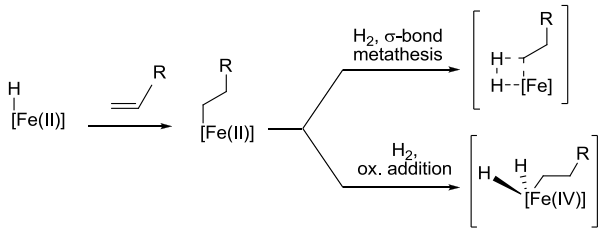
[158] P. J. Chirik, K. Wieghardt, *Science* **2010**, *327*, 794.

[159] J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, **1987**.

[160] S. C. Bart, E. Lobkovsky, P. J. Chirik, *J. Am. Chem. Soc.* **2004**, *126*, 13794; S. C. Bart, K. Chlopek, E. Bill, M. W. Bouwkamp, E. Lobkovsky, F. Neese, K. Wieghardt, P. J. Chirik, *J. Am. Chem. Soc.* **2006**, *128*, 13901; R. J. Trovitch, E. Lobkovsky, E. Bill, P. J. Chirik, *Organometallics* **2008**, *27*, 1470; S. K. Russell, J. M. Darmon, E. Lobkovsky, P. J. Chirik, *Inorg. Chem.* **2010**, *49*, 2782.

functional theory calculations established that the formally Fe(0)-compound was actually the physical oxidation state of an iron(II)-compound, where the metal transferred two electrons to the bis(imino)pyridine ligand.[161] Therefore, the ligand was supposed to act as a "non-innocent" ligand, although, up to now, a mechanism that takes into account the "non innocent" nature of the ligand is still missing.

Complexes **117** were introduced for the reduction of alkenes by Peters,[162] who hypothesized a mechanism where, after the coordination and the insertion of the alkene in the Fe-H bond, the unusual two-electron redox Fe(II)/Fe(IV) would take place or, alternatively, a σ-bond metathesis (Scheme 3.1).



Scheme 3.1

Up to date, no methods for the asymmetric hydrogenation of C-C double bonds by homogeneous chiral iron catalysts appeared.

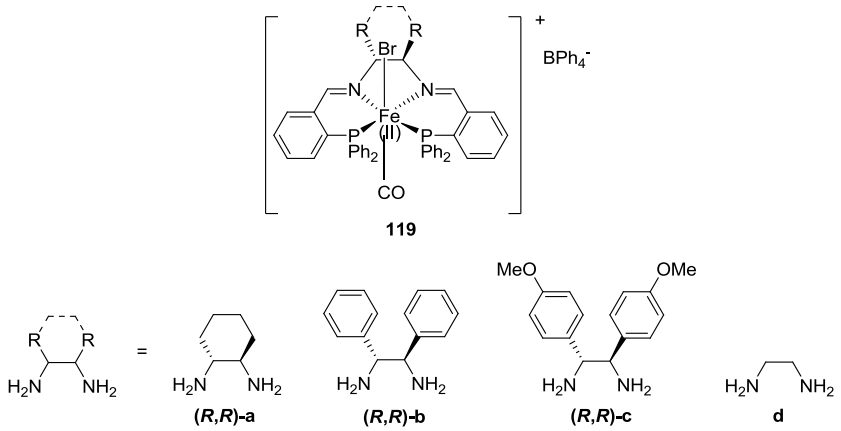
Iron-catalyst **118** was used by Bianchini to promote the reduction of terminal alkynes to the corresponding alkenes, although it was not active towards the olefin reduction.[163] It represents, up to now, the only example of well-defined homogeneous iron catalyst for the hydrogenation of triple C≡C bonds.

3.3 Iron-catalyzed reduction of C-X multiple bonds (ketones, aldehydes and imines)

The use of iron-catalysts for the reduction of the C=X bond (X = O or NR), has become more usual than its use in the C=C or C≡C hydrogenation, also including examples of enantioselective catalysts.

[161] J. P. Chirik, K. Wieghard, *Science* **2010**, *327*, 794; S. Stieber, E. Chantal, C. Milsmann, J. M. Hoyt, Z. R. Turner, K. D. Finkelstein, K. Wieghardt, S. DeBeer, J. P. Chirik, *Inorg. Chem.* **2012**, *51*, 3770; A. M. Tondreau, S. Stieber, E. Chantal, C. Milsmann, E. Lobkovsky, T. Weyhermuller, S. Semproni, J. P. Chirik, *Inorg. Chem.* **2013**, *52*, 635.
[162] E. J. Daida, J. C. Peters, *Inorg. Chem.* **2004**, *43*, 7474.
[163] C. Bianchini, A. Meli, M. Perruzzini, P. Frediani, C. Bohanna, M. A. Esteruelas, L. A. Oro, *Organometallics* **1992**, *11*, 138.

A key player in this field is certainly Morris, who prepared Fe(II)-complexes **119** bearing different bridging diamines, and tested their reactivity in transfer hydrogenation reactions.[164]



The bigger was the bulkiness of the diamine backbone, the higher were turnover frequency (TOF), catalytic activity and enantioselectivity of the complexes.

The key of the mechanism of these complexes lies in the "non-innocent" nature of the P,N,N,P-ligand, whose imino function is partially reduced to generate the catalytically active species. Here the diiminodiphosphino ligand, actively participating in the mechanism of C=O reduction by mediating the proton transfer, closely resembles the mechanism described by Noyori for his Ru(II)-catalyst[165] (Figure 3.1).

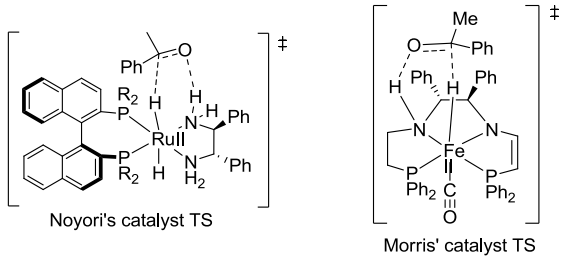
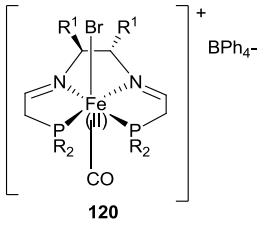


Figure 3.1

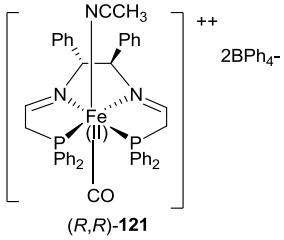
[164] A. A. Mikhailine, R. H. Morris, *Inorg. Chem.* **2010**, *49*, 11039.
[165] C. A. Sandoval, T. Ohkuma, K. Muniz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490; R. Noyori, M. Kitamura, T. Ohkuma, *Proc. Natl. Ac. Sci*. **2004**, *101*, 5356.

In addition, Morris developed the iron-complexes **120a**, **b**, **c**, and the related chiral complexes (*S*,*S*)-**120d**, **e**, **f**.[166]



120

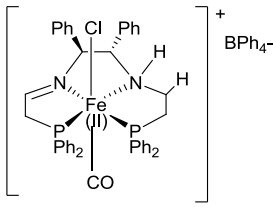
a: R = Cy, R^1 = H (*S*,*S*)-**d**: R = Cy, R^1 = Ph
b: R = *i*Pr, R^1 = H (*S*,*S*)-**e**: R = *i*Pr, R^1 = Ph
c: R = Et, R^1 = H (*S*,*S*)-**f**: R = Et, R^1 = Ph



(*R*,*R*)-**121**

Morris had also previously reported the complex (*R*,*R*)-**121**,[167] which showed higher activity and enantioselectivity in the transfer hydrogenation of acetophenone compared to complexes **120**, among which only the two complexes bearing the ethyl group at phosphorus (**120c** and (*S*,*S*)-**120f**) were active.

In a very recent report, again Morris *et al.* described the synthesis of a series of iron(II)-complexes **122** of partially saturated amine(imine)diphosphine (P,NH,N,P) ligands and their application to the asymmetric reduction of ketones and imines.[168] They ended up with the choice of selective non symmetrical ligands, after that species **122** revealed to be more reactive that the previously studied species **119b**.

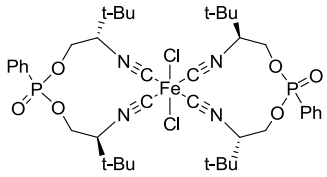


122

Unlike complex **119b**,[164,169] with complex **122** an induction period was not observed, and the rate of conversion at the chosen temperature (T = 28 °C) was substantially higher. TOF up to 6100 s^{-1} with complete conversion were observed, and enantiomeric excess up to 98% for ketone reduction and up to 99% for imine reduction were obtained.

[166] P. O. Lagaditis, A. J. Lough, R. H. Morris, *Inorg. Chem.* **2010**, 49, 10057.
[167] A. Mikhailine, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2009**, *131*, 1394.
[168] W. Zuo, A. J. Lough, Y. F. Li, R. H. Morris, *Science* **2013**, *342*, 1080.
[169] R. H. Morris, *Chem. Soc. Rev.* **2009**, *38*, 2282; P. E. Sues, A. J. Lough, R. H. Morris, *Organometallics* **2011**, *30*, 4418; A. A. Mikhailine, P. O. Lagaditis, A. J. Lough, R. H. Morris, J. Am. Chem. Soc. **2011**, *133*, 9666.

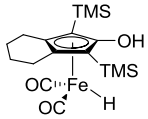
Also Reiser gave a contribution in iron-based catalysis, describing complex **123** prepared from two equivalents of a bis(isonitrile)ligand and $FeCl_2$. This complex showed good activity in the transfer hydrogenation of aromatic ketones as well as of heterocaromatic ketones with enantioselectivities up to 91%.[170]



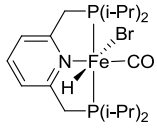
123

For this complex, a Meerwein-Ponndorf-Verley-type mechanism was proposed on the basis of IR and NMR studies. In this process, the formation of an iron hydride does not take place; rather, the *in situ* reduction of the isonitrile ligand to imine occurs, through the extraction of a hydride from isopropanol and following hydride transfer to the substrate.

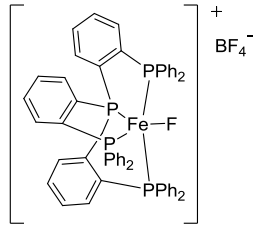
Highly effective achiral catalysts for the hydrogenation of ketones, aldehydes and imines are complexes **125**, **126** and **127**, developed by Knölker,[171] Casey,[172] Milstein[173] and Beller[174,175] respectively.



125



126

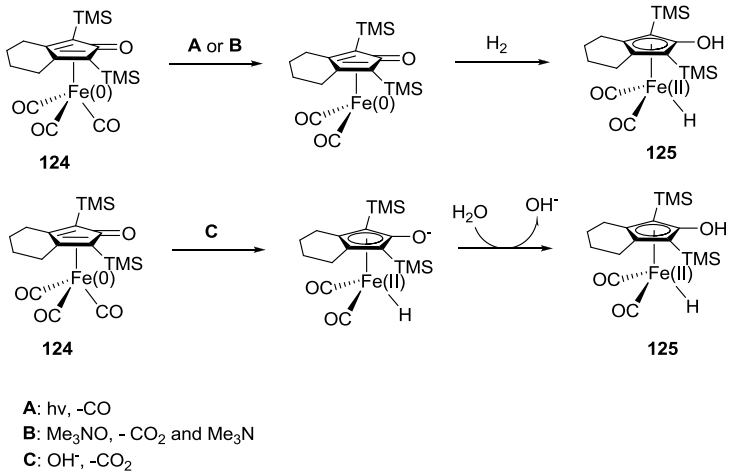


127

Catalyst **125** is very air- and moisture-sensitive, but three different routes were exploited by three research groups for its advantageous *in situ* formation. Starting from the stable

[170] A. Naik, T. Maji, O. Reiser, *Chem. Commun.* **2010**, *46*, 4475.
[171] H.-J. Knölker, E. Baum, H. Goesmann, R. Klauss, *Angew. Chem. Int. Ed.* **1999**, *38*, 2064.
[172] C. P. Casey, H. Guan, *J. Am. Chem. Soc.* **2007**, *129*, 5816; C. P. Casey, H. Guan, *J. Am. Chem. Soc.* **2009**, *131*, 2499.
[173] R. Langer, G. Leitus, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2011**, *50*, 2120; R. Langer, M. A. Iron, L. Kostantinovski, Y. Diskin-Posner, G. Leitus, Y. Ben-David, D. Milstein, *Chem. Eur. J.* **2012**, *18*, 7196.
[174] A. Tlili, J. Schranck, H. Neumann, M. Beller, *Chem. Eur. J.* **2012**, *18*, 15935; S. Fleischer, S. Zhou, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 5120;.S. Fleischer, S. Zhou, S. Werkmeister, K. Junge, M. Beller, *Chem. Eur. J.* **2013**, *19*, 4997.
[175] A. Boddien, D. Mellmann, F. Gärtner, R. Jackstell, H. Junge, P. J. Dyson, G. Laurenczy, R. Ludwig, M. Beller, *Science* **2011**, *333*, 1733; C. Ziebart, C. Federsel, P. Anbarasan, R. Jackstell, W. Baumann, A. Spannenberg, M. Beller, *J. Am. Chem. Soc.* **2012**, *134*, 20701; G. Wienhöfer, F. A. Westerhaus, K. Junge, R. Ludwig, M. Beller, *Chem. Eur. J.* **2013**, *19*, 7701.

precatalyst **124**, Berkessel used photolysis under controlled conditions to remove one CO ligand (**A**),[176] Renaud treated **124** with trimethylamine *N*-oxide (**B**),[177] while Beller exploited the so-called Hieber-base reaction (**C**)[178,179] (Scheme 3.2).



Scheme 3.2

Complex **126**, developed by Milstein and co-workers, catalyzes the hydrogenation of ketones under mild conditions making use of a metal-ligand cooperation, based on aromatization-dearomatization of the heteroaromatic core of the pincer tridentate P,N,P-ligand.[180] This is an example of "non-innocent" ligand behavior, where the ligand assists the metal center by undergoing reversible structural changes in the processes of substrate activation and product formation.

In complex **127**, in analogy to catalyst **118** proposed by Bianchini,[163] there is a P_4-tetradentate ligand. The Fe(II)-complex was developed by Beller for the hydrogenation of allylic aldehydes and CO_2, and the dehydrogenation of formic acid.[175]

[176] A. Berkessel, S. Reichau, A. von der Höh, N. Leconte, J.-M. Neudörfl, *Organometallics* **2011**, *30*, 3880.
[177] A. Pagnoux-Ozherelyeva, N. Pannetier, M. D. Mbaye, S. Gaillard, J. L. Renaud, *Angew. Chem. Int. Ed.* **2012**, *51*, 4976.
[178] W. Hieber, F. Leutert, *Anorg. Allg. Chem.* **1932**, *204*, 145.
[179] S. Fleischer, S. Zhou, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 5120; A. Tlili, J. Schranck, H. Neumann, M. Beller, *Chem. Eur. J.* **2012**, *18*, 15935.
[180] R. Langer, G. Leitus, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2011**, *50*, 2120; R. Langer, M. A. Iron, L. Kostantinovski, Y. Diskin-Posner, G. Leitus, Y. Ben-David, D. Milstein, *Chem. Eur. J.* **2012**, *18*, 7196.

3.4 Iron-catalysts for epoxidation reactions

Asymmetric epoxidation of olefins is one of the most important transformations in organic synthesis, since the resulting enantiomerically enriched epoxides are highly useful intermediates and building blocks.[181] Many iron catalysts have been developed for the epoxidation of olefins. They can be easily classified in two families: the first one includes the *iron-porphyrin-based complexes*, while the latter the *non-heme complexes*.

The iron-porphyrin-based complexes were the first iron-catalysts introduced in the epoxidation reaction, with the first example described in 1983 by Groves and Myers.[182] Later on, several research groups developed novel chiral iron complexes of this type for the asymmetric epoxidation of olefins.[183] However, several problems are correlated to the metalloporphyrin chemistry. Indeed, the synthesis of the chiral porphyrin core is crucial because the overall conversion is in general very low and the essential extensive purification implies great efforts. Moreover, a careful choice of the reaction conditions is needed during the linkage of chiral auxiliary. Another important limitation of these methodologies is that the oxidant is most often iodosylbenzene, which is not really considered environmentally friendly.

These limitations have thwarted the development of these porphyrin complexes for asymmetric epoxidation. On the other hand, all the features above listed, prompted the design of non-porphyrin chiral iron catalysts.

The first example of chiral non-heme iron complex was reported in 1999 by Francis and Jacobsen, who used an elaborate combinatorial screening of 5760 metal-ligand combinations to identify three peptide-like ligands suitable for Fe-catalyzed asymmetric epoxidation of *trans*-β-methylstyrene[184] (Scheme 3.3).

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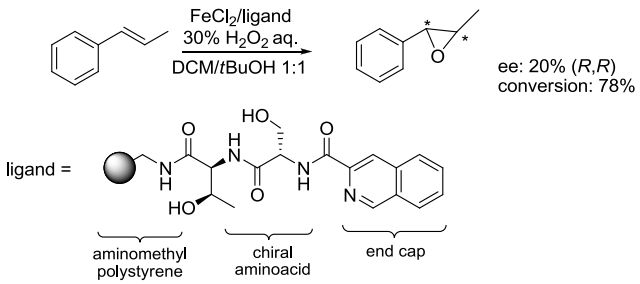
[181] B. S. Lane, K. Burgess, *Chem. Rev.* **2003**, *103*, 2457; Q. H. Xia, H. Q. Ge, C. P. Ye, Z. M. Liu, K. X. Su, *Chem. Rev.* **2005**, *105*, 1603; O. A. Wong, Y. Shi, *Chem. Rev.* **2008**, *108*, 3958; G. De Faveri, G. Ilyashenko, M. Watkinson, *Chem. Soc. Rev.* **2011**, *40*, 1722.

[182] J. T. Groves, R. S. Myers, *J. Am. Chem. Soc.* **1983**, *105*, 5791.

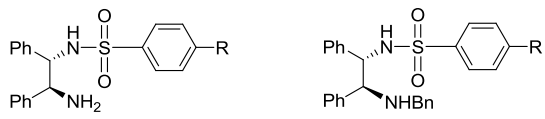
[183] Examples of chiral auxiliaries linked to porphyrin via amide bonds: D. Mansuy, P. Battioni, J-P. Renaud, P. J. Guerin, *Chem. Soc., Chem. Commun.* **1985**, 155; J. P. Collman, X. Zhang, V. J. Lee, J. I. J. Brauman, *Chem. Soc., Chem. Commun.* **1992**, 1647; E. Rose, M. Quelquejeu, R. P. Pandian, A. Lecas-Nawrocka, A. Vilar, G. Ricart, J. P. Collman, Z. Wang, A. Straumanis, *Polyhedron* **2000**, *19*, 581; Examples of chiral auxiliaries linked to porphyrin via ether bonds: Y. Naruta, F. Tani, K. Maruyama, *Tetrahedron. Lett.* **1992**, *33*, 6323; H. Nakagawa, Y. Sei, K. Yamaguchi, T. Nagano, T. J. Higuchi, *Tetrahedron: Asymmetry* **2004**, *15*, 3861; Examples of chiral auxiliaries linked to porphyrin via carbon-carbon bonds: G. Reginato, L. Di Bari, P. Salvadori, R. Guilard, *Eur. J. Org. Chem.* **2000**, 1165.

[184] M. B. Francis, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **1999**, *38*, 937.



Scheme 3.3

Some years later, Beller developed simple catalytic systems using commercially available enantiopure 1,2-diphenylethylenediamine.[185] The diamine was monosulfonylated to obtain one set of ligands (*S*,*S*)-**128** and the other free amino group was benzylated to get another set of ligands (*S*,*S*)-**129**. These chiral ligands were complexed with ferric chloride and pyridine-2,6-dicarboxylic acid (Pydic) as a co-ligand. The epoxidation reactions were carried out with 30% H_2O_2 at room temperature.



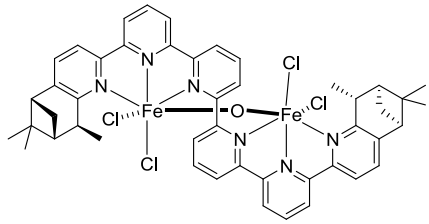
(*S*,*S*)-128
a: R = Me
b: R = Ph
c: R = *t*Bu

(*S*,*S*)-129
a: R = Me
b: R = Ph
c: R = *t*Bu

Ligand (*S*,*S*)-**129a** resulted in the best catalyst, giving excellent results with sterically bulky 4,4'-disubstituted *trans*-stilbenes (100% conversion, yield up to 90%, ee up to 91%).

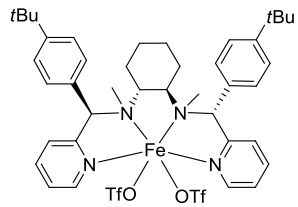
In 2008, Kwong described a new class of iron catalyst based on sexipyridines for epoxidation using H_2O_2.[186] Treatment of the ligand with $FeCl_2$ in 1:2 molar ratio afforded the binuclear species [Fe_2O(**130**)Cl_4], which was isolated as an air-stable solid. The diiron system showed good reactivity towards terminal and 1,2-disubstituuted aromatic alkenes, but induced low enantioselectivities (31−43%).

[185] F. G. Gelalcha, B. Bitterlich, G. Anilkumar, M. K. Tse, M. Beller, *Angew. Chem., Int. Ed.* **2007**, *46*, 7293; F. G. Gelalcha, G. Anilkumar, M. K. Tse, A. Brückner, M. Beller, *Chem.-Eur. J.* **2008**, *14*, 7687.
[186] H-L. Yeung, K-C. Sham, C-S. Tsang, T-C. Lau, H-L. Kwong, *Chem. Commun.* **2008**, 3801.



130

Sun developed the chiral iron(II)-complexes **131** using an N_4-ligand based on the ethylenediamine backbone, and displaying remarkable levels of enantioselectivity in the asymmetric epoxidation of α,β-enones, using hydrogen peroxide or peracetic acid as the oxidant (Scheme 3.4).[187]



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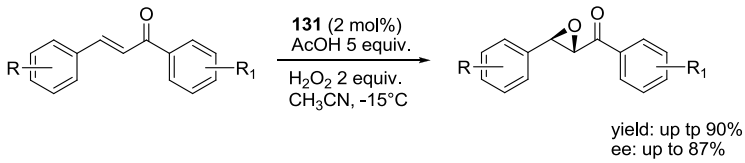
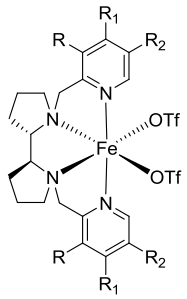


Scheme 3.4

Very recently, Costas described the use of non-heme iron complexes **132a-g** for the epoxidation of olefins with H_2O_2 as the oxidant, and improvement of the enantiomeric excess was attained by the use of carboxylic acid as additive, in particular acetic acid.[188] With *cis*-β-methylstyrene as substrate, the best results were obtained using complex **132a**, achieving the desired product in 87% yield and 62% ee when the reaction was carried out in the presence of a catalytic amount of CH_3COOH, in CH_3CN, for 30 minutes at -30°C. In the paper was also highlighted how electronic effects can be used as powerful tools for controlling the activation of H_2O_2 and O-atom transfer in non-porphyrine iron complexes.

[187] M. Wu, C-X. Miao, S. Wang, X. Hu, C. Xia, F. E. Kühn, W. Sun, *Adv. Synth. Catal*. **2011**, *353*, 3014.
[188] O. Cussó, I. Garcia-Bosch, X. Ribas, J. Lloret-Fillol, M. Costas, *J. Am. Chem. Soc.* **2013**, *135*, 14871.



a: R=R$_2$ = H, R$_1$ = NMe$_2$
b: R=R$_2$ = Me, R$_1$ = OMe
c: R=R$_2$ = H, R$_1$ = OMe
d: R=R$_2$ = H, R$_1$ = Me
e: R=R$_2$ = H, R$_1$ = H
f: R=R$_2$ = H, R$_1$ = Cl
g: R=R$_2$ = H, R$_1$ = CO$_2$Et

132

The positive role of acetic acid in iron-catalyzed oxidations has been documented for some years. Indeed, in many examples its presence has been shown to result in an increase in both catalytic activity and selectivity towards epoxidation, and also in the inhibition of *cis*-dihydroxilation versus epoxidation.[189] However, mechanistic interpretation has not been provided until recently.

A rationale for the Fe-catalyzed AcOH-assisted epoxidation of olefins with H_2O_2 was proposed by Que,[190] involving the intermediacy of an oxocarboxylate-iron(V) species (**b**) as the oxygen atom delivering agent (Scheme 3.5). Species **b** is formed *via* acid-assisted heterolytic cleavage of the O−O bond in a Fe(III)(OOH)-(HOAc) (**a**) precursor.

Experimental spectroscopic evidences in favor of this mechanistic scenario were also recently provided by Talsi, Bryliakov and co-workers,[191] and further computational support for the formation and oxidative competence of these species has been built by Rajaraman in a study for the ortho-hydroxylation of aromatic compounds by non-heme Fe complexes.[192]

[189] M. C. White, A. G. Doyle, E. N. Jacobsen, J. *Am. Chem. Soc.* **2001**, *123*, 7194; M. Fujita, L. Que Jr., *Adv. Synth. Cat.* **2004**, *396*, 190.
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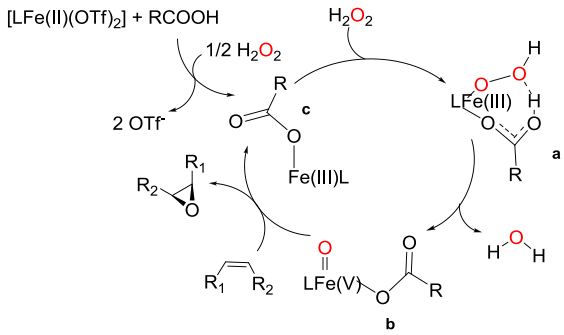

Scheme 3.5

3.5 Polydentate N_x ligands (tri- and tetradentate) for iron-catalyzed reactions

For the applications reported above, the catalysts employed were mainly Fe(II) or Fe(0) complexes.

We focused our attention on Fe(II). Regrettably, Fe(II)-complexes cannot be often considered as robust catalysts. Indeed, Fe(II) is very prone to oxidation to Fe(III), and for this reason Fe(II)-complexes usually need to be handled under extra-dry and oxygen-free conditions. Moreover, NMR spectroscopy, commonly used by chemists as a technique for structural characterization, can be rarely used for Fe(II)-complexes, which are in most cases paramagnetic. For these the characterization often relies on mass spectrometry (ESI being the most suitable ionization methodology) and X-ray diffraction.

As shown in the sections above, the best way to stabilize the reactive Fe(II) metal centre is the use of polydentate ligands, which provide the desired stabilization by means of kinetic (steric) and thermodynamic (entropic) effects.

In particular, we turned our attention to polydentate N-ligands, (tri- and tetradentates), based on the following considerations:

- N-ligands are good sigma-donor ligands and are expected to stabilize the relatively hard Fe(II) more efficiently than P-ligands,
- they are easier to prepare and more stable than P-ligands; indeed these are themselves often prone to oxidation, especially in the case of electron-rich phosphines.

3.5.1 Tridentate N_3-ligands

Among the different types of tridentate nitrogen ligands, we focused our attention on scorpionate ligands.

This new versatile class of ligands appeared in 1966, showing peculiar features typical of cyclopentadienyl ligands.[193] Like the pincer of a scorpion, these tripodal ligands generally bind metal centers with nitrogen atoms from two pyrazole rings attached to the central atom (e.g. boron); the third pyrazole attached to central atom (e.g. boron) rotates forward like a scorpion's tail to "sting" the metal; hence the name of "scorpionates" (Figure 3.2).

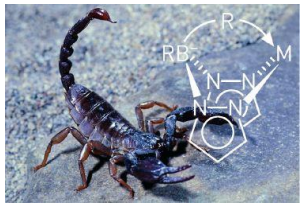

Figure 3.2

Over the years, the definition of scorpionates has been extended to tripodal ligands analogs to tris(pyrazol-1-yl)borates with different donor groups and bridging atoms. Central atoms other than boron, such as carbon, silicon, germanium, tin, aluminium, gallium, indium, phosphorus and nitrogen have been reported,[194] even though the most studied classes of scorpionates are the B-centered tris(pyrazol-1-yl)borate derivatives and the C-centered tris(pyrazol-1-yl)alkane derivatives.[195]

The ligand are commonly 6 electron donors and occupy three coordination sites as capping ligands when binding to the metal (Figure 3.3).

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[195] S. Trofimenko, *J. Am. Chem. Soc.* **1970**, *92*, 5118; D. L. Reger, *Comm. Inorg. Chem.* **1999**, *21*, 1; A. Otero, J. Fernandez-Baeza, A. Antinolo, J. Tejeda, A. Lara-Sanchez, *Dalton Trans.* **2004**, 1499; H. R. Bigmore, S. C. Lawrence, P. Mountford, C. S. Tredget, *Dalton Trans.* **2005**, 635; C. Pettinari, R. Pettinari, *Coord. Chem. Rev.* **2005**, *249*, 525.

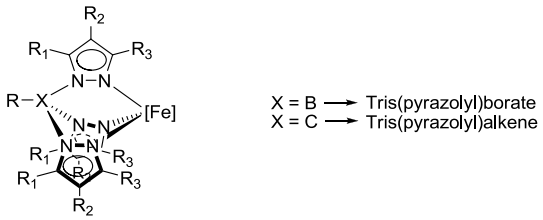

Figure 3.3

Tris(pyrazol-1-yl)borates and tris(pyrazol-1-yl)alkanes have been extensively investigated in inorganic, bioinorganic and organometallic chemistry,[196,197] and numerous reviews on their coordination properties with s,p-block elements[198] and transition metals[195,199] have been reported.

In general, independently of the nature of the bridging atom, two families of scorpionate ligands may be distinguished, namely *homoscorpionates* and *heteroscorpionates*, according to the presence of one or more types of metal binding groups, respectively.

In this chapter we will deal only with the first type, possessing a local C_{3v} symmetry.

The naming of homoscorpionates follows some general rules.[200]

When R is H (Figure 3.3), the abbreviation **Tp** for tris(pyrazol-1-yl)borates and **Tm** for tris(pyrazol-1-yl)methanes is used.

Then, the substituents are denoted by superscripts. The "default" position in this abbreviation system is the 3-position on the pyrazole ring, which is denoted by a superscript "R_1", that is Tp^{R_1}. Thus, for instance, hydrotris(3-methylpyrazol-1-yl)borate is denoted as Tp^{Me}. The 5-substituent follows the 3-substituent as a superscript, separated by a comma. For instance, hydrotris(3-isopropyl-5-methylpyrazol-1-yl)borate is denoted as $Tp^{iPr,Me}$. When both 3 and the 5 substituents are identical, the superscript substituent is followed by a 2: for instance hydrotris(3,5-dimethylpyrazol-1-yl)borate is Tp^{Me_2}. A substituent in the 4-position is denoted as a $4R_1$ superscript. Thus, hydrotris(3-methyl-4-bromopyrazol-1-yl)borate is $Tp^{Me,4Br}$. All the rules described so far are valid for Tm derivatives as well.

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[196] S. Trofimenko, *Scorpionates: The Coordination Chemistry of Poly(pyrazolyl)borate Ligands.* Imperial College Press: London. (**1999**)
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[200] S. Trofimenko, *Chem. Rev.* **1993**, *93*, 943.

The coordination properties of scorpionates strictly depend on the steric and electronic effects of the substituents on pyrazoles.[201] In general, scorpionates include a wide set of coordination modes in addition to the typical k^3-N,N',N''.[202] They can, in fact, behave as tridentate k^3-N,N',X-H donors,[203] with a borohydride moiety linked to the metal, as bidentates k^2-N,N'[204] or k^2-N,X-H,[205] and more rarely, as k^1 and k^0 (*i.e.* as uncoordinated counterion).[206] Higher denticities (k^6 and occasionally k^4 and k^5) are possible in case the substituents in 3-position of the pyrazole rings contain additional donor atoms[207] (Figure 3.4).

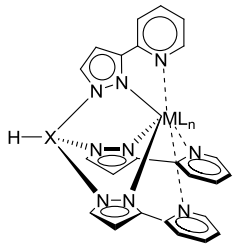

Figure 3.4

The use of pyrazoles with bulky substituents may prevent the formation of a octahedral homoleptic ML_2 complexes (L = Tp or Tm) **133**, and rather prefer the formation of a half-sandwich complex **134**. Complexes **133**, typical of Tp and Tm derivatives of pyrazoles bearing small substituents or without any substituents, are formed in high yields by mixing iron(II) salts, as $FeCl_2$, $Fe(OAc)_2$ and $Fe(OTf)_2$, with two equivalents of non-bulky ligands (e.g. Tp_2Fe and $Tp^{Me2}{}_2Fe$).[208]

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[201] N. Kitajima, W. B. Tolman, *Progr. Inorg. Chem.* **1995**, *43*, 419.
[202] F. T. Edelmann, *Angew. Chem. Int. Ed.* **2001**, *40*, 1656.
[203] N A. Kremer-Aach,W. Kläui, R. Bell, A. Strerath, H. Wunderlich, D. Mootz, *Inorg. Chem.* **1997**, *36*, 1552.
[204] R. G. Ball, C. K. Ghosh, J. K. Hoyano, A. D. McMaster, W. A. G. Graham, *J. Chem. Soc., Chem. Commun.* **1989,** *1989*, 341; U. E. Bucher, A. Currao, R. Nesper, H. Rueegger, L. M. Venanzi, E. Younger, *Inorg. Chem.* **1995**, *34*, 66; V. Chauby, C. S. LeBerre, P. Kalck, J. C. Daran, G. Commenges, *Inorg. Chem.* **1996**, *35*, 6354.
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[206] E. Gutierrez, S. A. Hudson, A. Monge, M. C. Nicasio, M. Paneque, E. Carmona, *J. Chem. Soc., Dalton Trans.* **1992**, 2651; M. Paneque, S. Sirol, M. Trujillo, E. Gutierrez-Puebla, M. A. Monge, E. Carmona, *Angew. Chem. Int. Ed.* **2000**, *39*, 218.
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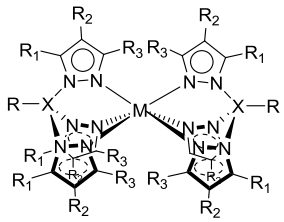

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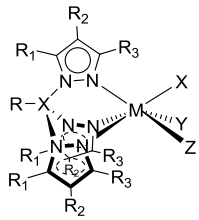
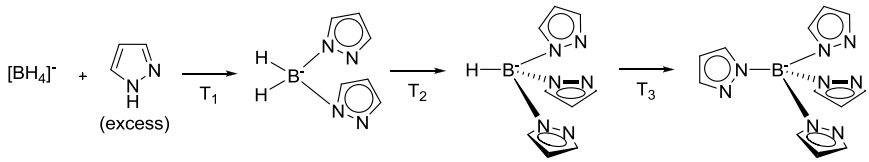


134

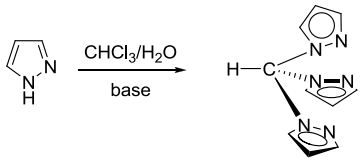
Homotris(pyrazol-yl)borates can be synthesized by many different routes,[196] but most easily by reaction of the proper pyrazole with a borohydride anion in the absence of solvent (Scheme 3.6).



Scheme 3.6

As shown in Scheme 3.6, temperature control steers the reaction to produce selectively only one of the above products. A large variety of 1-H pyrazoles may be employed to synthesize poly(pyrazolyl)borates by this route, with the exception of those containing functionalities incompatible with the borohydride ion.

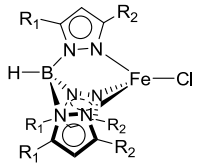
Tris(pyrazol-1-yl)methanes are, instead, mainly prepared as shown in Scheme 3.7.

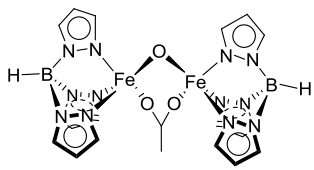


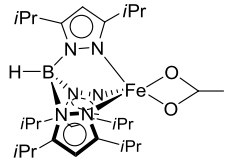
Scheme 3.7

Examples of iron complexes with scorpionates already well studied and characterized in literature are, for instance, the Fe(II)-complexes **135** ($Tp^{tBu,Me}FeCl$, $Tp^{Ph,Me}FeCl$, $Tp^{iPr_2}FeCl$) obtained from $FeCl_2$ and one equivalent of the Tp ligand.[209]

[209] F. A. Jové, C. Pariya, M. Scoblete, G. P. A. Yap, K. H. Theopold, *Chem. Eur. J.* **2011**, *17*, 1310; T. Tietz, C. Limberg, R. Stößer, B. Ziemer, *Chem. Eur. J.* **2011**, *17*, 10010.







135 **a**: R_1 = Me, R_2 = *t*Bu
b: R_1 = Me, R_2 = Ph
c: R_1 = *i*Pr, R_2 = *i*Pr

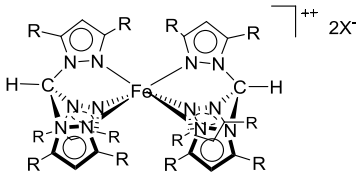
136

137

Oxo-bridged diiron centers, such as $Tp_2Fe_2(\mu\text{-}O)(\mu\text{-}O_2CCH_3)$ **136**, that resembles metalloenzymes such as hemerythrin, rubrerythrin, and methane momo-oxygenase, were also prepared.[210] The five-coordinate iron(III) complex $Tp^{iPr}Fe(OAc)$ **137** is another example of Tp-iron complex, that acts as a mimic for non-heme metalloprotein hemoglobin and cytochrome P-450.[211]

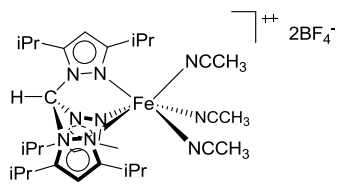
Tris(pyrazol-yl)methane iron complexes have also been studied since they were for the first time synthesized by Trofimenko, but not as extensively as the analogous tris(pyrazolyl)borate iron complexes.[194] Iron complexes of Tm ligands, such as $[Tm_2Fe][X_2]$ **138**, where X is: BF_4^-, ClO_4^-, OTf^-, can be formed in high yields using the corresponding iron(II) salts ($Fe(BF_4)_2$, $Fe(ClO_4)_2$, $Fe(OTf)_2$) with two equivalents of Tm ligand. These iron(II) complexes have also displayed unusual temperature-dependent spin-state crossover behavior similar to that of their Tp_2Fe analogs.[212]

Similarly, Tm-type iron complexes of considerable interest are the facially-capped synthons. One example is the complex $[Tm^{Me2}Fe(NCCH_3)_3]$ $[(BF_4)_2]$ **139**.[213]



R = H or Me

138



139

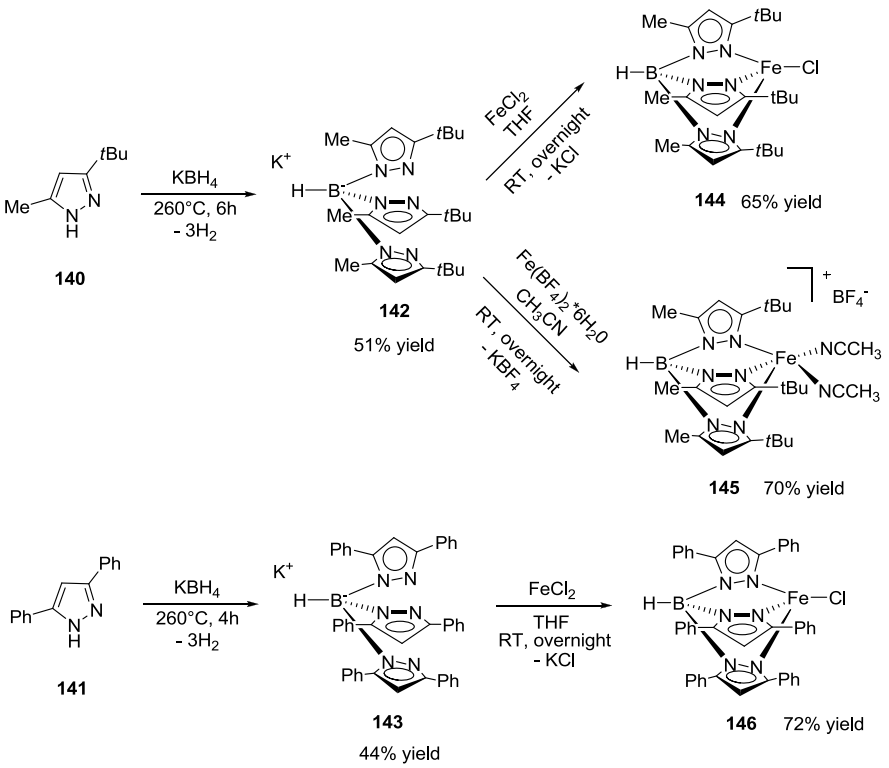
[210] J. S. Loehr, W. D. Wheeler, A. K. Shiemke, B. A. Averill, T. M. Loehr, *J. Am. Chem. Soc.* **1989**, *111*, 8084.
[211] N. Kitajima, N. Tamura, H. Amagai, H. Fufui, Y. Moro-oka, Y. Mizutani, T. Kitagawa, R. Mathur, K. Heerwegh, C. A. Reed, C. R. Randall, L.J. Que, K. Tatsumi, *J. Am. Chem. Soc.* **1994**, *116*, 9071.
[212] D. L. Reger, C. A. Little, A. L. Rheingold, M. Lam, L. M. Liable-Sands, B. Rhagitan, T. Concolino, A. Mohan, G. L. Long, V. Briois, F. Grandjean, *Inorg. Chem.* **2001**, *40*, 1508; M. A. Goodman, A. Y. Nazarenko, B. J. Casavant, Z. Li, W. W. Brennessel, M. J. DeMarco, G. Long, M. S. Goodman, *Inorg. Chem.* **2012**, *51*, 1084.
[213] P. G. Edwards, A. Harrison, P. D. Newman, W. Zhang, *Inorg. Chim. Acta* **2006**, *359*, 3549.

Our aim was to apply some scorpionate iron complexes as catalysts for the hydrogenation of double bonds, for which no examples have been ever reported.

In order to have active catalyst species, we chose as starting point pyrazoles bearing bulky substituent, to avoid the formation of octahedral Tp_2Fe or $[Tm_2Fe][2X^-]$ complexes.

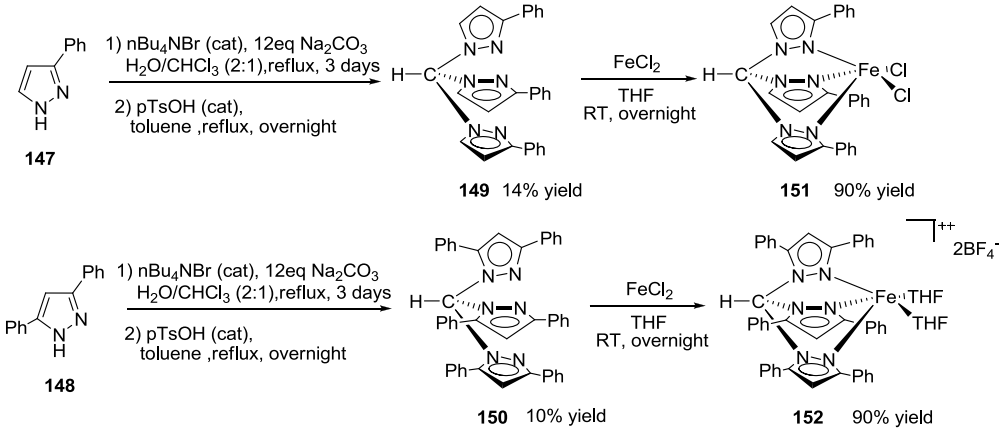
All the chosen pyrazoles are commercially available, except 3-*tert*-butyl-5-methylpyrazole, that was synthetized by a condensation reaction between the corresponding β-diketone and hydrazine. Tris(pyrazol-yl)borates were prepared through a neat reaction at high temperature, from an excess of pyrazoles (more than 3 equivalents) and KBH_4. The borates were obtained in relatively good yield. Instead, tris(pyrazol-yl)methanes were prepared by reacting 3 equivalents of the desired pyrazoles in a basic mixture of $H_2O/CHCl_3$. Unfortunately the latter ligands were obtained in low yield.

From tris(pyrazol-yl)borates we synthesized two neutral TpFeCl complexes, $Tp^{tBu,Me}FeCl$ **144** and $Tp^{Ph_2}FeCl$ **146**, by reaction of 1 equivalent of the chosen KTp ligand with 1 equivalent of $FeCl_2$, in THF at room temperature. The cationic complex $[Tp^{tBu,Me}Fe][BF_4]$ **145** was prepared by reaction of the $KTp^{tBu,Me}$ ligand with one equivalent of $Fe(BF_4)_2*6H_2O$ in CH_3CN at room temperature (Scheme 3.8).



Scheme 3.8

In addition, we synthetized also two tris(pyrazol-yl)methane complexes: neutral $Tm^{Ph}FeCl_2$ **151**, from the corresponding Tm^{Ph} ligand and $FeCl_2$ in THF at room temperature; dicationic $[Tm^{Ph_2}Fe][2BF_4]$ **152** from Tm^{Ph_2} ligand, using this time $Fe(BF_4)_2*6H_2O$ as iron(II) source (Scheme 3.9).

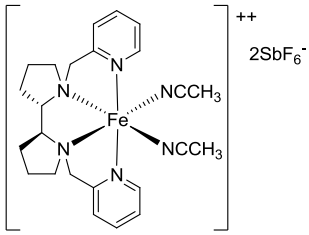


Scheme 3.9

These ligands have been exclusively investigated by us in the hydrogenation reaction of C=C and C=N double bonds.

3.5.2 Tetradentate N_4-ligands

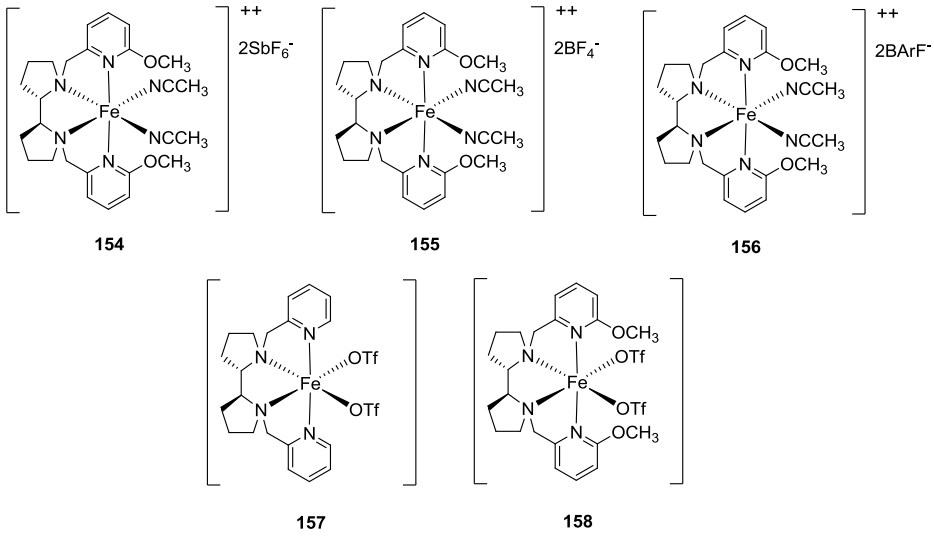
As tetradentate N_4-ligands we prepared a series of derivatives of the complex **153**, developed by White *et al.*,[214] who used it for selective C–H bond oxidations with high chemo- and stereoselectivity. Complex **153** was described as an easy-to-prepare air- and moisture-stable compound.



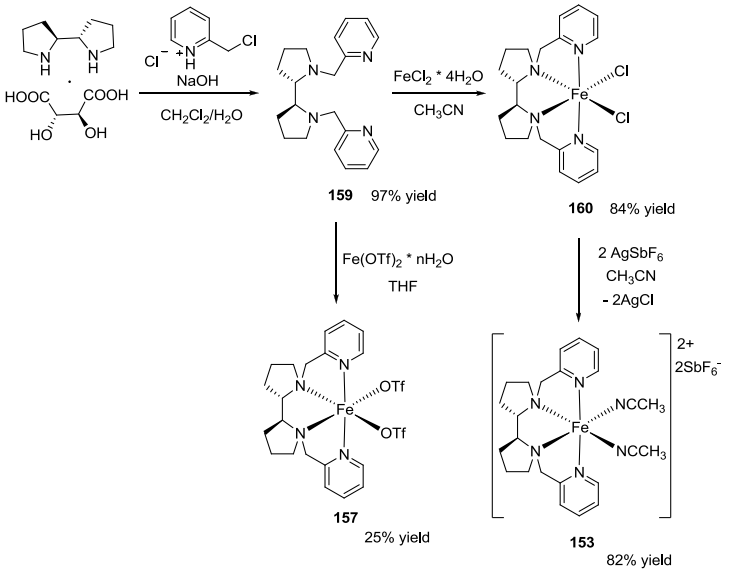
153

Complex **153** has a modular structure that allowed the preparation of the following derivatives: **154**, **155**, **156**, **157**, **158**, that we decided to investigate as catalysts for both the hydrogenation and the epoxidation reactions.

[214] M. S. Chen, M. C. White, *Science* **2007**, *318*, 783; N. A. Vermeulen, M. S. Chen, M. C. White, *Tetrahedron* **2009**, *65*, 3078; M. S. Chen, M. C. White, *Science* **2010**, *327*, 566.

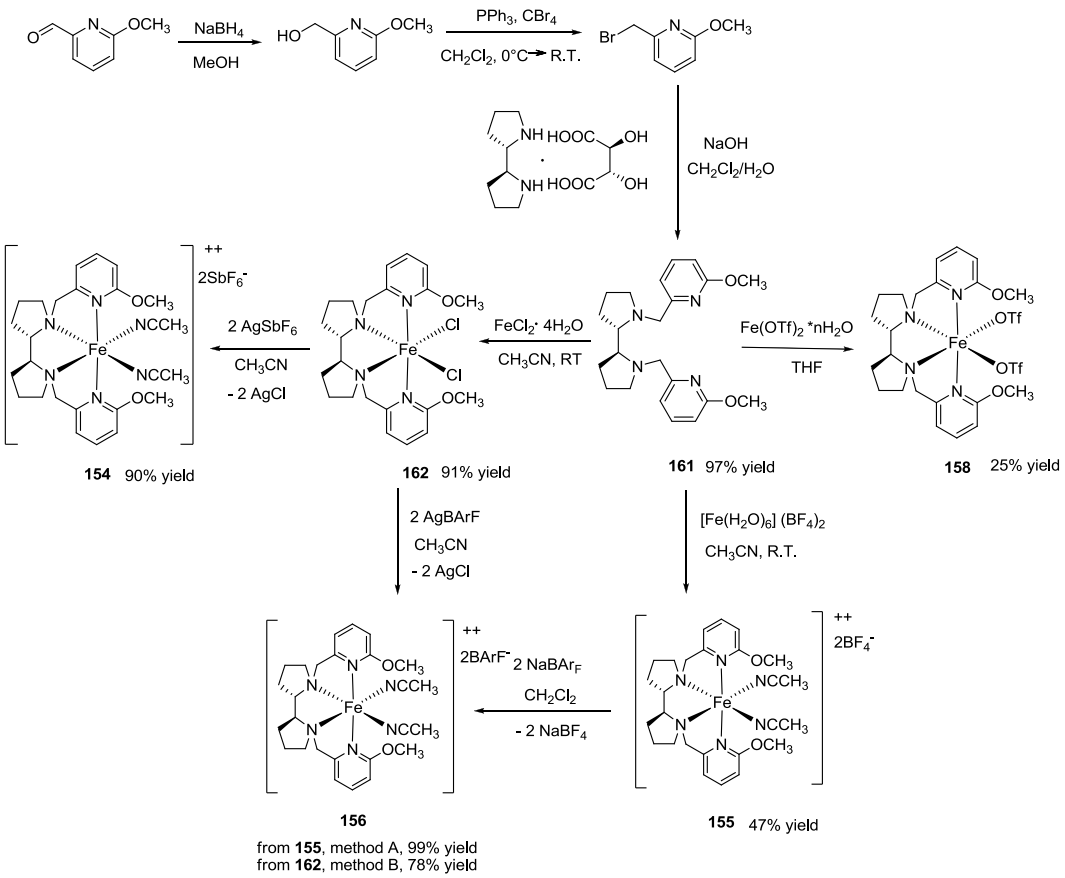


This class of octahedral complexes consists of an iron(II) coordinated to the tetradentante chiral ligand which leaves available two more coordination sites in *cis* position.[215]
Their synthesis is shown in Scheme 3.10 and Scheme 3.11.



Scheme 3.10

[215] S. E. Denmark, J. Fu, M. J. Lawler, S. Lee, E. Huntsman, E. J. J. Grabowski, *Org. Synth.* **2006**, *83*, 121.



Scheme 3.11

Complex **154**, the analog of **153** bearing -OMe groups in the *ortho* position of the pyridine rings, was prepared in order to study the effect of the substituent on the activity/selectivity. Since **154** showed solubility only in CH_3CN, similar complexes with BF_4 (**155**) and BArF (**156**) counteranions were prepared. Indeed, complex **155** showed solubility also in CH_3OH, while complex **156** is soluble in several common organic solvents (CH_3CN, CH_3OH, CH_2Cl_2, THF, toluene).

Complex **157** (Scheme 3.10) was used by Costas *et al.* as catalyst for the epoxidation of *cis*-β-methylstyrene, and complex **158** was prepared by us in order to investigate if the substituent in the two *ortho* positions could lead to an increase of activity and/or selectivity, as observed by Costas with the correlated *meta*- or *para*-OMe derivative.[188]

3.6 Catalytic applications

3.6.1 Reduction of C=C and C=X double bonds

First of all, we decided to start with the investigation of the complexes as catalysts for the hydrogenation of functionalized alkenes. With this aim, we chose a benchmark substrate, methyl-2-acetamidoacrylate **163**, and then we screened our iron-complexes, both the tridentate N_3- and the tetradentate N_4-ligands.

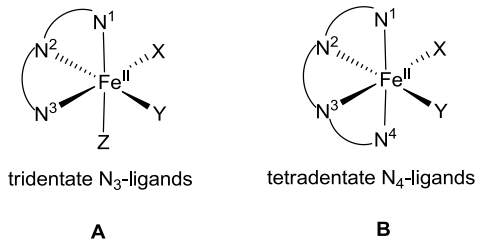
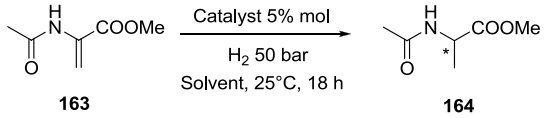


Figure 3.5

The potential reactivity of the two classes of complexes in Figure 3.5 relies for type **A** in the three "free" coordination sites in adjacent position, while for type **B** in the two "free" coordination sites in *cis*-position. The sites are in principle useful for the H_2 activation, in order to have the formation of a hypothetic Fe-H bond, and the coordination of the substrate.



163 **164**

All the reaction were carried out with 5 mol% of catalyst loading, at 50 bar of H_2 pressure, at 25°C, for 18 hours.

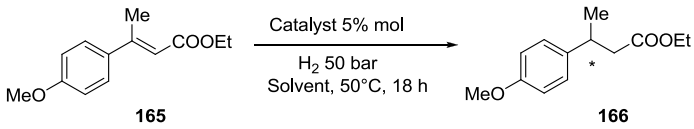
All the scorpionate-complexes were tested, i.e. the neutral complexes of **144**, **146**, **151** the monocationic **145** and the dicationic **152**. Unfortunately, neither in CH_2Cl_2, nor in THF the complexes led to any conversion. Together with them, also the neutral dichloro complex of the N_4-tetradentate ligand, **160**, and the White's complex **153**, were investigated. In this case,

not only CH_2Cl_2 and THF, but also toluene, CH_3OH and CH_3CN were screened as solvents. Regretfully, in all cases only the starting alkene was recovered.

The following step was to check if complexes with a better solubility (i.e. with tetrafluoroborate or tetrakis[3,5-bis(trifluoromethyl)phenyl]borate as counteranion), could ride over the lack of reactivity. Hence, again the complexes **144** and **145** were used as catalyst, but this time together with an equimolar quantity of AgBArF in order to lead to the *in situ* counteranion exchange (with the precipitation of AgCl) and formation of a cationic Fe(II) species, in principle more active thanks to the exchange of the chloride anion with the bulky, weakly coordinating, highly lipophilic BArF anion. Besides also the pre-synthesized derivatives of complex **153**, namely **155** and **156**, with respectively BF_4^- and $BArF^-$ as counteranion, were tested as for **144** and **145** in CH_2Cl_2, but also in THF and toluene, due to their initial solubility even in the less polar solvents. Here again the conversion still did not differ significantly from 0.

As last attempt on this substrate, the five neutral complexes **144**, **146**, **151**, **160**, **162**, which are the chlorine-derivatives, were investigated in the reaction carried out in CH_2Cl_2 with the addition of a Grignard (EtMgBr), respectively 10 mol% with **144** and **146**, and 20 mol% with **151**, **160**, **162**, in order to form once again a more reactive species *in situ*, in particular, in this case, an iron(0) species.[216] Regrettably, only the unreacted starting product was recovered.

The possible activity of complex **144** was also investigated with another functionalized alkene, **165**.

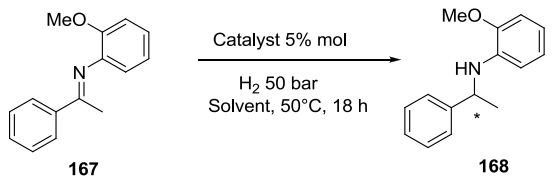


165 **166**

The reaction was carried out at 50°C, for 18 hours at 50 bar of hydrogen pressure, but neither in CH_2Cl_2 nor in isopropanol, afforded the reduced product **166**.

Concerning the reduction of C=X double bonds, very preliminary attempts were made with substrate **167**, just to test again the reactivity of complex **144**.

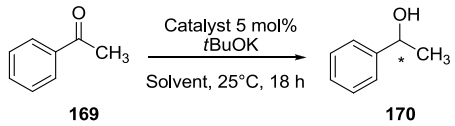
[216] B. Bogdanovic, M. Schwickardi, *Angew. Chem., Int. Ed.* **2000**, *39*, 4610; A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130* , 8773.



167 **168**

So, the tris(3-*tert*-butyl-5-methyl-pyrazoyl)borate iron complex was used as catalyst in the reaction carried out both in CH_2Cl_2 and in *i*PrOH with the addition 50 mol% of a base (*t*BuOK). Unfortunately this complex revealed to be inactive also for the hydrogenation of the imine **167**.

Then we moved onto ketone transfer hydrogenation, choosing acetophenone **169** as the benchmark substrate.



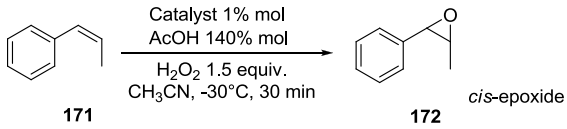
169 **170**

All the reaction were carried out at 25 °C for 18 hours. Only some complexes of the class of N_4-tetradentate ligands were used for this reaction. The dicationic catalyst **153** as well as the neutral catalyst **160**, formed from the same N_4-tetradentate ligand, were selected.
The reactions were carried out in pure *i*PrOH, with a base/catalyst ratio of 0 (i.e., no base), 10, 100 and in a mixture of *i*PrOH/CH_3CN 1:2 or *i*PrOH:CH_2Cl_2 1:2. No conversion was observed, except when the reaction was carried out in *i*PrOH with a base/catalyst ratio of 100 (in which case conversion was less than 5%).

3.6.2 Epoxidation

Prompted by recently exiting results reported by Costas,[188] we were willing to screen our N_4-tetradentate ligand complexes, in particular those of ligand **161**, with two *ortho*-OMe groups on the pyridine rings.
Costas reported the application of iron(II) bis-triflate complexes where the ligand's pyridine rings bear substituents in *para*-position. For this reason, we prepared complex **158**, as

reported in Scheme 3.11, and examined its reactivity in the epoxidation reaction of *cis*-β-methylstyrene **171**, the same substrate studied by Costas.



Entry	Catalyst	Conversion[a] (%)	ee[b] (%)
1	**158**	10	5
2	**153**	87	19
3	**154**	12	5

[a] Determined by ^{1}H-NMR and GC
[b] Determined by GC, column MEGADEX DACTBSβ
Table 3.1

The reactions were carried out in the presence of 1 mol% of catalyst, 1.4 equivalent of AcOH, and an excess of hydrogen peroxide, at -30 °C for 30 min.

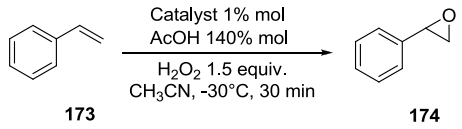
Besides complex **158**, we investigated also complexes **153** and **154**, that are the bis(hexafluoroantimonate) iron(II)-complexes of ligand **159** and **161**.

Complex **153** gave good results, comparable to the results obtained by Costas with the bis-triflate complex **157**.[188]

Unfortunately, the introduction of a -OMe group in *ortho*-position of the pyridine rings led to a dramatical drop in terms of conversion and enantioselectivity (entries 1 and 3) and also the formation of several unidentified side products.

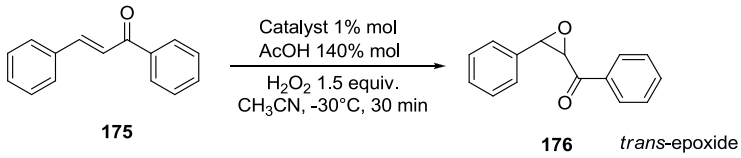
Prolonged reaction times, up to 24 hours, did not lead to an improvement in terms of conversion and enantiomeric excess.

Then styrene **173** was subjected to the same conditions to test the activity of complexes **157** and **158**.



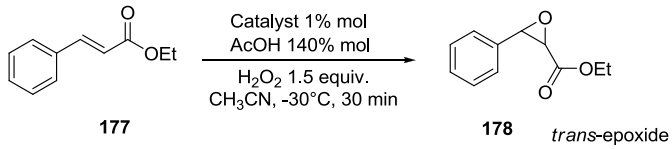
Also for this substrate, complex **157** bearing unsubstituted pyridine rings, revealed to be a good catalyst. Indeed very good results in terms of conversion were achieved, although the

enantiomeric excess was low (conversion 100%, ee 8%). On the contrary, complex **158** led once again to unsatisfactory results (conversion 10%, ee 0%) and to the formation of several unidentified side products.



175 **176** *trans*-epoxide

Under the same conditions, the epoxidation of chalcone **175** (an α,β-unsatured ketone), with catalysts **158** led to a mixture of unidentified side products, among which the desired oxide product, in very poor amount. This reaction was not further investigated.



177 **178** *trans*-epoxide

Similarly, ethyl cinnamate was not a good substrate for these catalysts and conditions: both complex **157** and **158**, were not able to convert substrate **177** into its epoxidation product **178**.

3.7 Conclusion

In this chapter we discussed the formation of iron(II)-complexes from polydentate nitrogen ligands, suitable for the stabilization of a very unstable Fe(II) towards the oxidation to Fe(III).

Tridentate N_3-ligands and tetradentate N_4-ligands were prepared and reacted with Fe(II)-sources and the resulting complexes were subjected to hydrogenation, transfer hydrogenation and epoxidation reactions.

The purification of the complexes was sometimes arduous, because some of them were partially soluble even in the most apolar solvents such as hexane and pentane. Moreover, the characterization of the complexes was not easy, as little information could be drawn from ^{1}H-NMR spectroscopy (due to the paramagnetism of octahedral iron-complexes) and had to rely on mass spectrometry (altough mass spectra were sometimes difficult to interpret).

The iron-complexes prepared so far did not afford promising results, probably due to the stereoelectronic properties of our ligands since they appeared as not the most suitable complexes for these applications.

Perhaps the substitution of some N-coordinated atoms with phosphines, which in general affects the hardness and the capability of accepting π-backdonation from metals in low oxidation states, would make the complexes more catalytically active, in particular for reduction applications.

Further studies are currently ongoing in our laboratory to modify the ligand structures and achieve conversion and e.e.'s.

3.8 Experimental section

General Remarks

All reactions were carried out under a nitrogen atmosphere, except the synthesis of complexes that was performed under argon atmosphere, using standard Schlenk-techniques.

The reactions were performed with distilled solvents. The solvents for reactions were distilled over the following drying agents and transferred under nitrogen: CH_2Cl_2 (CaH_2), MeOH (CaH_2), CH_3CN (CaH_2), THF (Na), dioxane (Na), toluene (Na), hexane (Na), Et_3N (CaH_2). Acetophenone and *i*-PrOH were distilled on CaH_2 (a small amount of PPh_3 was added when distilling isopropanol) and stored over molecular sieves. Et_2O and DMF were purchased in bottles with crown cap, over molecular sieves, and stored under nitrogen.

Air sensitive liquids and solutions were transferred via a gas-tight syringe or cannula.

Removal of solvents was accomplished by evaporation on a Buchi rotary evaporator (water bath 40°C) or directly from the Schlenk using an oil pump.

The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness). Visualisation was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution or a nynhidrine solution. Flash column chromatography was performed using silica gel (60 Å, particle size 40-64 μm) as stationary phase, following the procedure by Still and co-workers.[217] Gas chromatography was performed by a GC instrument equipped with a flame

[217] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

ionization detector, using the chiral capillary column MEGADEX DACTBSβ, diacetyl-*t*-butylsilyl-β-cyclodextrin.

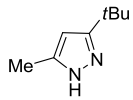
^{1}H- and ^{13}C-NMR spectra were recorded measured on a Bruker DRX 400MHz. Chemical shifts are reported in ppm with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded with a 400 MHz spectrometer operating at 100.56 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.23 ppm).

High resolution mass spectra were measured with a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics)-4.7 T Magnet (Magnex) equipped with ESI source. Low resolution mass spectra (MS) were acquired either on a Thermo-Finnigan LCQ Advantage mass spectrometer (ESI ion source).Chiral HPLC analysis were performed with a Shimadzu instrument equipped with a Diode Array detector. Elemental analyses were performed on a Perkin Elmer Series II CHNS/O Analyzer 2000. Infrared spectra were recorded on a standard FT/IR spectrometer.

Commercially available reagents were used as received without, unless indicated otherwise.

3.8.1 Synthesis of the ligands and relative precursors

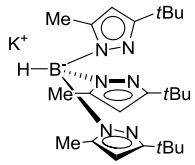
3-*tert*-butyl-5-methylpyrazole (**140**)



Compound **140** was synthesized according to a published procedure.[218,219]

Yield: 75% - **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H), 2.27 (s, 3H), 5.87 (s, 1H), 8.80 (bs, 1H). Spectroscopic data of the product were in agreement with the literature.[220]

Potassium tris(3-*tert*-butyl-5-methyl-1H-pyrazol-1-yl)hydroborate (**142**)

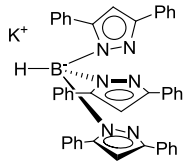


[218] F. Swamearnd, C. Hauser, *J. Am. Chem. Soc.* **1950**, *72*, 1352**.**
[219] A. Mukherjee, U. Subramanyam, V. G. Puranik, T. P. Mohandas, A. Sarkar, *Eur. J. Inorg. Chem.* **2005**, 1254.
[220] A. Alberola, A. González-Ortega, M. L. Sádaba, M. C. Sañudo *J. Chem. Soc., Perkin Trans. 1*, **1998**, 4061.

Ligand **142** was synthesized according to a published procedure.[221]

Yield: 51% - **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.30 (d, 27H, *J* = 10.1), 2.37 (s, 3H), 5.80 (d, 1H, *J* = 12.6 Hz). Spectroscopic data of the product were in agreement with the literature.

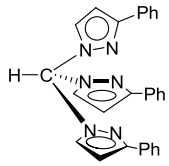
Potassium tris(3,5-diphenyl-1H-pyrazol-1-yl)hydroborate (**143**)



Ligand **143** was synthesized according to a published procedure.[222]

Yield: 44% - **^{1}H NMR** (400 MHz, CD_2CO): δ = 6.75 (s, 3 H), 6.95-7.50 (m, 18 H), 7.80-7.95 (m, 12 H). Spectroscopic data of the product were in agreement with the literature.

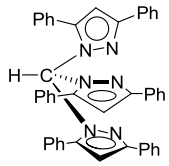
Tris(3-phenyl-1H-pyrazol-1-yl)methane (**149**)



Ligand **149** was synthesized according to a published procedure.[223]

Yield: 15% - **^{1}H NMR** (400 MHz, CD_2CO): δ = 6.90 (d, 3H, *J* = 2.4 Hz), 7.35 (tt, 3H, *J* = 1.2, 2.8 Hz), 7.38-7.44 (m, 6H), 7.88-7.92 (m, 6H), 8.10 (d, 3H, *J* = 2.4 Hz), 8.86 (s, 1H). Spectroscopic data of the product were in agreement with the literature.

Tris(3,5-diphenyl-1H-pyrazol-1-yl)methane (**150**)

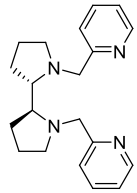


Ligand **150** was synthesized according to a published procedure.[224]

[221] S. Trofimenko, J. C. Calabrese, J. K. Kocbi, S. Wolowiec, F. B. Hulsberger, J. Reedijk, *Inorg. Chem.* **1992**, *31*, 3943.
[222] Kitajima N., Moro-oka Y., Kitagawa T., Tatsumi K., *J. Am. Chem. Soc*. **1992**, *114*, 1277.
[223] D. L. Reger, T. C. Grattan, K. J. Brown, C. A. Little, J. J.S. Lamba, A. L. Rheingold, R. D. Sommer, *J. Organomet. Chem.* **2000**, *607*, 120.
[224] M. Kujime, T. Kurahashi, M. Tomura, H. Fujii, *Inorg. Chem.* **2007**, *46*, 541.

Yield: 10% - **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.57 (3H, s), 6.81 (d, 6H, *J* = 7.1 Hz), 7.14 (t, 6H, *J* = 7.7 Hz), 7.22-7.29 (m, 6H), 7.34 (t, 6H, *J* = 7.5 Hz), 7.80 (d, 6H, *J* = 7.0 Hz), 7.82 (s, 1H). Spectroscopic data of the product were in agreement with the literature.

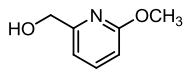
(2*S*,2'*S*)-1,1'-Bis(pyridin-2-ylmethyl)-2,2'-bipyrrolidine (**159**)



Ligand **159** was synthesized according to a published procedure.[225]

Yield: 97% - **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.68-1.91 (m, 8H), 2.14-2.32 (q, 2H, *J* = 8.6 Hz), 2.76-2.82 (m, 2H), 2.98-3.08 (m, 2H), 3.53 (d, 2H, *J* = 14.4 Hz), 4.21 (d, 2H, *J* = 14.0 Hz), 7.12 (dd, 2H, *J* = 7.0, 5.2 Hz), 7.42 (d, 2H, *J* = 7.8 Hz), 7.61 (td, 2H, *J* = 7.6, 1.7 Hz), 8.52 (d, 2H, *J* = 4.2 Hz). Spectroscopic data of the product were in agreement with the literature.

2-(Hydroxymethyl)-6-methoxypyridine

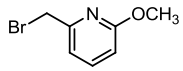


$NaBH_4$ (96%, 0.85 g, 21.6 mmol) was added portionwise to a stirred solution of 6-methoxy-2-pyridinecarboxaldehyde (1.04 g, 7.37 mmol) in 20 mL MeOH kept at 0 °C. The reaction mixture was stirred at RT for 3 hours, then distilled H_2O was added and MeOH was evaporated. The aqueous layer was extracted with CH_2Cl_2, the collected organic phases were washed with brine, dried with Na_2SO_4 and filtered. Evaporation of solvents afforded a pale yellow liquid in 98% yield, which was used in the following step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (bs, 1H), 3.89 (s, 3H), 4.64 (s, 2H), 6.59 (d, 1H, *J* = 8.2 Hz), 6.80 (d, 1H, *J* = 7.2 Hz), 7.51 (t, 1H, *J* = 7.7 Hz). Spectroscopic data of the product were in agreement with the literature.[226]

[225] M. S. Chen, M. C. White, *Science* **2007**, *318*, 783.
[226] A. Belen, M. Fatemeh, J. Gurnos, P. Caroline, N. G. Nadine, W. Jonathan, *Tetrahedron* **1988**, *44*, 3005.

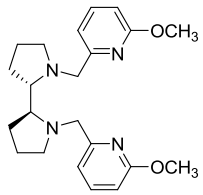
2-(Bromomethyl)-6-methoxypyridine



CBr_4 (3.61 g, 10.8 mmol) and PPh_3 (2.83 g, 10.8 mmol) were added in sequence to a stirred solution of **15** (1.00 g, 7.18 mmol) in 18 mL CH_2Cl_2 kept at 0 °C. Upon addition of the triphenylphosphine the solution became purple/brown. The reaction mixture was allowed to warm up at room temperature and was stirred for 2 hours, after which period a whitish precipitate was present. Solvents were evaporated to give a brown oil, which was purified by flash chromatography eluting with hexane/AcOEt 98:2. The product was obtained in 80% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (s, 3H), 4.48 (s, 2H), 6.67 (d, 1H, *J* = 8.4 Hz), 7.00 (d, 1H, *J* = 7.2 Hz), 7.56 (t, 1H, *J* = 7.8 Hz). Spectroscopic data of the product were in agreement with the literature.[227]

(2*S*,2'*S*)-1,1'-Bis((6-methoxypyridin-2-yl)methyl)-2,2'-bipyrrolidine (*S*,*S*-PDP-OMe) (**161**)



NaOH (512 mg, 12.8 mmol) and 2-(bromomethyl)-6-methoxypyridine (1137 mg, 5.6 mmol) dissolved in 9 mL CH_2Cl_2 were added in sequence to a stirred suspension of (*S*,*S*)-2,2'-bipyrrolidine D-tartrate trihydrate (890 mg, 2.6 mmol) in 9 mL H_2O. The obtained biphasic mixture was stirred overnight at room temperature, then diluted with 1M NaOH and extracted with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4, filtered and concentrated in vacuo to obtain a sticky yellow oil.

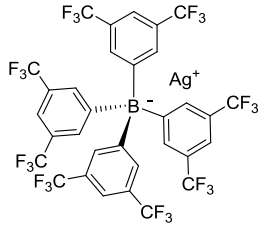
The crude was purified by flash chromatography eluting with CH_2Cl_2/MeOH/aqueous NH_3 (33%) 97:3:2. The collected fractions were combined, diluted with CH_2Cl_2, washed with 1M NaOH and dried with Na_2SO_4. Evaporation of solvents afforded the product in 97% yield as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (t, 2H, *J* = 7.6 Hz), 6.98 (d, 2H, *J* = 7.2 Hz), 6.57 (d, 2H, *J* = 8.0 Hz), 4.14 (d, 2H, *J* = 14.4 Hz), 3.91 (s, 6H), 3.45 (d, 2H, *J* = 14.4 Hz), 3.10 (m,

[227] C. Derong, J. Huanfeng, Z. Hong, L. Wenjie, Z. Hong, M. Herbert, *J. Org. Chem.* **2011**, *76*, 5531.

2H), 2.87 (bs, 2H), 2.29 (m, 2H), 1.68-1.90 (m, 8H) - **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.5, 158.2, 138.8, 115.3, 108.1, 65.2, 60.5, 55.3, 53.4, 26.2, 23.7.

Silver tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (AgBArF)



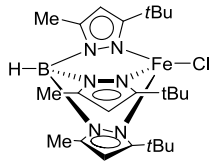
AgBArF was synthesized according to a published procedure.[228]

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 7.63 (s, 8H), 7.72 (s, 4H).

Spectroscopic data of the product were in agreement with the literature.

3.8.2 Synthesis of the complexes

Complex [Tp^{tBu,Me}FeCl] (**144**)

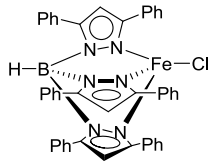


$FeCl_2$ (26 mg, 0.2 mmol) was added to a solution of Tp^{tBu,Me}K **142** (100 mg, 0.2 mmol) in THF (3 mL). The solution was stirred overnight at room temperature. Filtration over celite and removal of solvent under vacuum resulted in a dark yellow residue. Addition of pentane caused precipitation of a solid. The solvent was decanted off and the solid dried under high vacuum, affording complex **144** in 65% yield as a yellow solid. Spectroscopic data of the product were in agreement with the literature.[229]

^{1}H NMR (400 MHz, (C_6D_6): δ = - 11.1 (bs, 27H), 39.7 (bs, 9H), 50.0 (bs, 1H), 63.8 (bs, 3H) - **MS**: $[M\text{-}Cl]^+$ *m/z*: 479.5.

[228] E. Buschmann, J. S. Miller, K. Bowman-James, C. N. Miller, *Inorg. Synth.* **2002**, *33*, 83.
[229] F. A. Jové, C. Pariya, M. Scoblete, G. P. A. Yap, K. H. Theopold, *Chem. Eur. J.* **2011**, *17*, 1310.

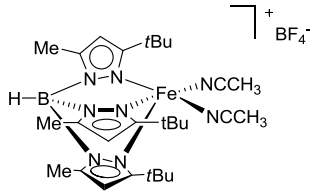
Complex [$Tp^{Ph2}FeCl$] (**146**)



$FeCl_2$ (28.4 mg, 0.22 mmol) was added to a solution of $Tp^{Ph2}K$ **143** (150 mg, 0.22 mmol) in THF (3 mL). The solution was stirred overnight at room temperature. Filtration over celite and removal of solvent under vacuum resulted in a pale yellow residue. Addition of pentane caused precipitation of a solid. The solvent was decanted off and the solid dried under high vacuum, affording complex **146** in 72% yield as a white solid.

MS: $[M\text{-}Cl]^+$ *m/z*: 725.5.

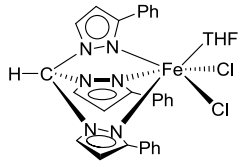
Complex [$Tp^{tBu,Me}Fe][BF_4$] (**145**)



$Fe(BF_4)_2{}^*6H_2O$ (174 mg, 0.52 mmol) was added to a solution of $Tp^{tBu,Me}K$ **142** (250 mg, 0.52 mmol) in CH_3CN (5 mL). The solution was left to stir overnight. Filtration over celite and removal of solvent under vacuum resulted in the complex **145** in 70% yield as a green solid.

MS: $[M(CH_3CN)_2]^+$ *m/z*: 561.3

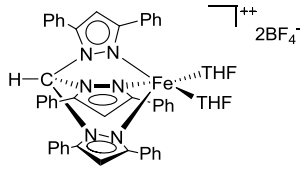
Complex [$Tm^{Ph}FeCl_2$] (**151**)



$FeCl_2$ (52 mg, 0.41 mmol) was added to a solution of Tm^{Ph} **149** (180 mg, 0.41 mol) in THF (4 mL). The solution was left to stir overnight. Removal of solvent under vacuum afforded complex **151** in 90% yield as a red solid.

MS: $[M(THF) + H]^+$ *m/z*: 641.3

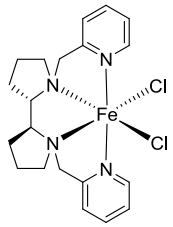
Complex [Tm^{Ph2}Fe][2BF_4] (**152**)



$Fe(BF_4)_2{}^*6H_2O$ (40 mg, 0.11 mmol) was added to a solution of Tm^{Ph2} **150** (70 mg, 0.11 mmol) in THF (3 mL). The reaction mixture was stirred overnight. Removal of the solvent under vacuum resulted in a pale yellow residue. Addition of pentane caused precipitation of a solid. The solvent was decanted off and the solid dried under high vacuum, affording complex **152** in 90% yield as a white solid.

MS: $[M(THF)_2]^{++}$ + MeOH *m/z*: 451.3

Complex [$FeCl_2$(S,S-PDP)] (**160**)

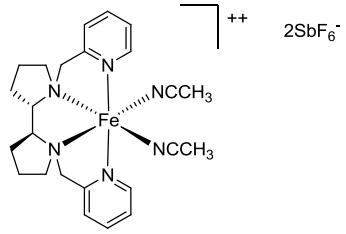


Complex **160** was synthesized according to a published procedure.[214]

MS: $[M\text{-}Cl]^+$ *m/z*: 413.3. - $C_{10}H_{11}N_3O_5$ (448.1): calcd. C 53.48; H 5.83; N 12.47; found C 53.14; H 5.95; N 12.45.

Spectroscopic data of the product were in agreement with the literature.

Complex [Fe(*S*,*S*-PDP)($CH_3CN)_2$][($SbF_6)_2$] (**153**)



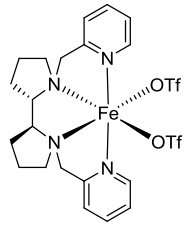
Complex **153** was synthesized according to a published procedure.[214]

^{1}H NMR (400 MHz, CD_3CN): δ = 0.1 (bs, 2H), 2.2 (bs, 8H), 3.5 (bs, 2H), 4.5 (bs, 2H), 8.5 (bs, 4H), 9.7 (bs, 2H), 10.8 (bs, 2H), 16.1 (bs, 2H), 17.0 (bs, 4H), 17.8 (bs, 1H), 43.8 (bs, 2H).

MS: $[M - CH_3CN]^{++}$ *m/z*: 209.5. **FT-IR** (Nujol): 2308.37 cm^{-1}, 2273.66 cm^{-1} (weak, $CH_3C{\equiv}N$ stretching).

Spectroscopic data of the product were in agreement with the literature.

Complex [Fe(*S*,*S*-PDP)($OTf)_2$] (**157**)

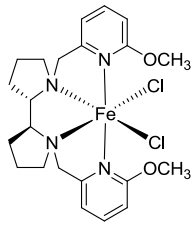


A solution of ligand **159** (278 mg, 0.71 mmol) in THF (3.5 mL) was added to a suspension of $Fe(OTf)_2{}^{*}nH_2O$ (85%) (295 mg, 0.84 mmol) in THF (3.5 mL) at room temperature with stirring. The mixture was stirred overnight and the solvent removed under vacuum to give a light brown powder. The residue was washed with Et_2O/hexane 1:1 (2 mL) and then hexane (2 mL). The solvent was decanted off and the solid dried under high vacuum, affording complex **157** in 25% yield as a yellow solid.

MS: $[M - OTf]^+$ *m/z*: 527.3.

Spectroscopic data of the product were in agreement with the literature.[230]

Complex [$FeCl_2$((*S*,*S*)-PDP-OMe)] (**162**)

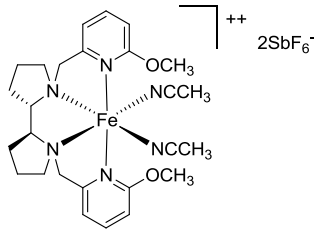


$FeCl_2{}^{*}4H_2O$ (273 mg, 1.37 mmol) was added to a stirred solution of ligand **161** (525 mg, 1.37 mmol) in 8 mL CH_3CN. The yellowish, slightly turbid solution was stirred overnight at room temperature. 10 mL Et_2O were added and a sticky brown solid precipitated. Solvents were decanted off and the residue was dried under high vacuum, then dissolved in CH_2Cl_2. Addition of pentane caused precipitation of a brown solid again. The solvents were decanted off and the solid was dried under high vacuum, giving complex **162** in 91% yield.

MS: $[M-Cl]^+$ *m/z*: 473.2.

[230] K. Suzuki, P. D. Oldenburg, L. Que, Jr., *Angew. Chem. Int. Ed.* **2008**, *47*, 1887.

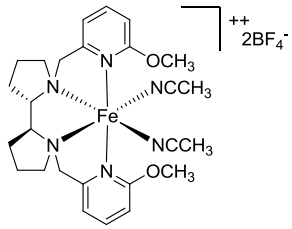
Complex [Fe(CH_3CN)$_2$(*S*,*S*-PDP-OMe)][2SbF_6] (**154**)



Silver hexafluoroantimonate (207 mg, 0.59 mmol) was added to a stirred thick brown solution of **162** (150 mg, 0.29 mmol) in 5 mL CH_3CN. The reaction mixture became beige and a white precipitate formed. The flask was covered with aluminum foil and the mixture was stirred overnight at RT. On the next day silver chloride was filtered off under Ar and the clear brown filtrate was evaporated to dryness. The residue was re-dissolved in CH_3CN, filtered through a 0.2 μm Acrodisc® LC PVDV syringe filter and concentrated. The filtration/evaporation procedure was repeated two more times to ensure no silver salts remains. The last time the filtrate was evaporated under N_2 stream and then under high vacuum, obtaining a brilliant brown solid in 90% yield.

^{1}H NMR (400 MHz, CD_3CN): δ = 1.82-1.93 (m, 2H), 1.95-2.08 (bs, 8H), 2.10-2.30 (m, 4H), 2.45 (bs, 2H), 3.50-3.59 (m, 2H), 3.59-3.68 (m, 2H), 3.88 (s, 6H), 4.12 (bs, 2H), 4.67 (d, 2H, *J* = 17.2 Hz), 4.81 (d, 2H, *J* = 17.2 Hz), 6.99 (d, 2H, *J* = 9.6 Hz), 7.11 (d, 2H *J* = 8.0 Hz), 8.02 (t, 2H, *J* = 7.4 Hz) - **MS**: $[M\text{-}2CH_3CN]^{2+}$ *m/z*: 219.5.

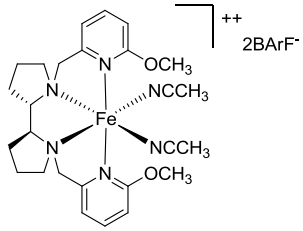
Complex [Fe((*S*,*S*)-PDP-OMe)(CH_3CN)$_2$][2BF_4] (**155**)



A solution of ligand **161** (300 mg, 0.78 mmol) in 10 mL CH_3CN was transferred via cannula into a stirred solution of iron(II) tetrafluoroborate hexahydrate (273 mg, 0.78 mmol) in 10 mL CH_3CN. The resulting pale yellow solution was stirred overnight at room temperature, then the solvent was evaporated and the yellow residue was washed with Et_2O, decanting off the solvent via syringe. Drying under high vacuum afforded complex **155** as a yellow-greenish solid in 47% yield.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.3 (bs, 2H), 2.39 (bs, 2H), 2.5-3.2 (m, 10H), 3.0 (bs, 2H), 4.03 (bs, 8H), 4.6-4.9 (m, 4H), 5.2 (bs, 2H), 6.7 (bs, 2H), 7.4 (bs, 2H), 8.1 (bs, 2H) - **MS**: $[M-2CH_3CN]^{2+}$ *m/z*: 219.3.

Complex [Fe((*S*,*S*)-PDP-OMe)($CH_3CN)_2$][2BAr_F] (**156**)



METHOD A

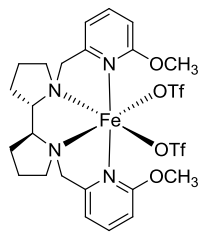
$NaBAr_F$ (230 mg, 0.26 mmol) was added to a stirred solution of complex **155** (90 mg, 0.13 mmol) in 10 mL CH_2Cl_2. The reaction mixture became turbid and, after stirring for 1 hour, was filtered through celite under Ar. Evaporation of the filtrate gave complex **156** as a whitish solid in 99% yield.

FT-IR (Nujol): 2306.45 cm^{-1}, 2277.52 cm^{-1} ($CH_3C{\equiv}N$ stretching).

METHOD B

$AgBAr_F$ (381 mg, 0.40 mmol) was added to a stirred thick brown solution of complex **162** (100 mg, 0.20 mmol) in 8 mL CH_3CN. Upon addition the reaction mixture became turbid and a white solid precipitated. The reaction mixture was stirred overnight with minimal light exposure and the precipitate was then filtered off under Ar. The filtrate was evaporated to dryness, the brown residue was taken up with 10 mL CH_3CN and filtered through a 0.2 μm Acrodisc® LC PVDV syringe filter. The evaporation/filtration procedure was repeated to ensure no silver salts remains. Evaporation of solvents afforded complex **156** as a dark brown solid in 78% yield.

Complex [Fe((*S*,*S*)-PDP-OMe)($OTf)_2$] (**158**)



A solution of ligand **161** (266 mg, 0.69 mmol) in THF (1.5 mL) was added to a suspension of $Fe(OTf)_2{}^{*}nH_2O$ (85%) (258 mg, 0.73 mmol) in THF (1.5 mL) at room temperature with stirring. The mixture was stirred overnight and the solvent removed under vacuum to give a light brown powder. The residue was washed with Et_2O/hexane 1:1 (2 mL) and then with hexane (2 mL). The solvent was decanted off and the solid dried under high vacuum, affording complex **157** in 25% yield as a yellow solid.
MS: $[M - OTf]^+$ *m/z*: 587.1.

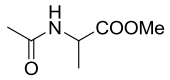
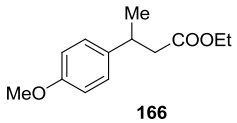
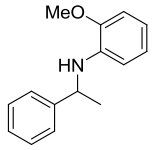
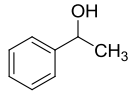
3.8.3 Hydrogenation and epoxidation reactions

- General procedure for the hydrogenation reactions

A Parr multireactor was employed, allowing six reactions in parallel under hydrogen pressure. The selected complex (5 mg, 0.05 eq) and the substrate (1 eq) were weighted in special glass vessels, which were then purged with nitrogen. Solvent (7 mL) was added via syringe, the vessels were placed in the respective autoclaves and purged three times with 50 bar of hydrogen. The reactions were stirred under hydrogen pressure at the desired temperature for a given time and then analyzed for conversion and ee determination, using ^1H NMR, GC or HPLC.

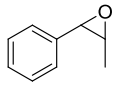
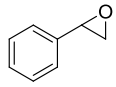
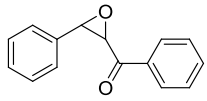
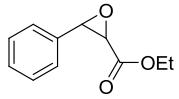
- General procedure for the transfer hydrogenation reactions

A carousel multireactor was employed, allowing eight reactions in parallel under nitrogen atmosphere. Under N_2 flow, the selected complex (4 mg, 0.05 eq) and the desired base (0.50 eq) were introduced in special glass vessels, which were then closed with screw caps and purged with nitrogen. Distilled isopropanol (2 mL) and acetophenone (10-20 μL, 1 eq) were added via syringe and the reactions were stirred under nitrogen at the desired temperature for a given time and then analyzed for conversion and ee determination, using ^1H NMR, GC or HPLC.

ENTRY	PRODUCT Spectral data match those previously reported.	SEPARATION METHOD
1	 **164** *Org. Lett.* **2010**, *12*, 1296.	GC (column MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin 0.25 μm; diameter = 0.25 mm; length = 25 m); carrier: hydrogen; Conditions: flow:1 mL/min; 140 °C for 6 min, then gradient 8 °C/min. $t_{substrate}$ = 3.9 min; t_R = 5.2 min; t_S = 6.0 min
2	 **166** *Tetrahedron : Asymmetry* **2011**, *22*, 47.	HPLC. Column Chiralpak AD -H, Heptane/IPA 99:1, flow 0.5 mL/min
3	 **168** *J. Am. Chem. Soc.* **2009**, *131*, 8358.	HPLC. Column Chiracel OD, Heptane/IPA 95:5, flow 0.5 mL/min
4	 **170** *Angew. Chem. Int. Ed.* **2012**, *51*, 12102.	GC (capillary column: MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin, 0.25 μm; diameter = 0.25 mm; length = 25 m) carrier: hydrogen; Conditions: hydrogen pressure:1 bar; 75 °C for 5 min, 20 °C/min gradient to 95 °C, 95 °C for 15 min, then gradient 20 °C/min. $t_{substrate}$ = 9.3 min; t_{ee1} = 17.5 min; t_{ee2} = 19.8 min.

- General procedure for the epoxidation reactions

A carousel multireactor was employed. To a solution of complex (2-2.5mg, 0.01 eq) in CH_3CN (3 mL), the substrate (0.11 M, 1 eq) was added and the solution stirred at room temperature. The the solution was cooled at -30 ºC, and AcOH was added (28 μL, 1.4 eq.) Then, 50 μL of 1:1 v:v acetonitrile:hydrogen peroxide solution 30 % (1.5 equiv.) was added by syringe pump over a period of 30 min or through 5 additions of 10 μL each over a period of 30 min by micropipette. The solution was further stirred at -30 ºC for 30 minutes. The reaction was quickly filtered through a basic alumina plug, which was subsequently rinsed with 2 x 1 mL EtOAc. ^{1}H-NMR and GC analysis of the solution provided substrate conversion and ee%. Spectroscopic data of the products were in agreement with the literature.

ENTRY	PRODUCT Spectral data match those previously reported.	SEPARATION METHOD
1	 **172** *cis*-epoxide *Angew. Chem. Int. Ed.* **2010**, *49*, 628.	GC (column MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin 0.25 μm; diameter = 0.25 mm; length = 25 m); carrier: hydrogen; Conditions: flow:3.5 mL/min; 75 °C for 5 min, then gradient: 3 °C/min to 90°C, then gradient: 7°C/min to 200°C $t_{substrate}$ = 3.6 min; t_R = 8.1 min; t_S = 9.6 min
2	 **174** *J. Am. Chem. Soc.* **1994**, *116*, 933.	GC (column MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin 0.25 μm; diameter = 0.25 mm; length = 25 m); carrier: hydrogen; Conditions: flow:3.5 mL/min; 75 °C for 5 min, then gradient: 3 °C/min to 90°C, then gradient: 7°C/min to 200°C $t_{substrate}$ = 2.1 min; t_R = 8.6 min; t_S = 9.1 min
3	 **176** *trans*-epoxide *Org. Lett.* **2009**, *16*, 3622.	HPLC. Column Chiracel OB, Heptane/IPA 9:1, flow 1.0 mL/min
4	 **178** *trans*-epoxide *J. Org. Chem.* **2009**, *74*, 3986.	HPLC. Column Chiracel OB, Heptane/IPA 9:1, flow 1.0 mL/min

Index

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